MILITARY MEDICAL MANUALS

GENERAL EDITOR:
SURGEON-GEN. SIR ALFRED KEOGH
G.C.B., M.D., F.R.C.P.

MALARIA IN MACEDONIA

ARMAND-DELILLE, ABRAMI
PAISSEAU & LEMAIRE

EDITED BY
SIR RONALD ROSS

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MALARIA IN MACEDONIA

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CLINICAL AND HÆMATOLOGICAL FEATURES AND PRINCIPLES OF TREATMENT

BY

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UNIVERSITY OF LONDON PRESS, LTD.
18 WARWICK SQUARE, LONDON, E.C.4
PARIS: MASSON ET CIE, 120 BOULEVARD SAINT-GERMAIN
1918

GENERAL INTRODUCTION

The infinite variety of injuries which any war presents to the surgeon gives to military surgery a special interest and importance. The special interest and importance, in a surgical sense, of the great European War lies not so much in the fact that examples of every form of gross lesion of organs and limbs have been seen, for if we read the older writers we find little in the moderns that is new in this respect but is to be found in the enormous mass of clinical material which has been presented to us and in the production of evidence sufficient to eliminate sources of error in determining important conclusions. For the first time also in any campaign the labours of the surgeon and the physician have had the aid of the bacteriologist, the pathologist, the physiologist, and indeed of every form of scientific assistance, in the solution of their respective problems. The clinician entered upon the great war armed with all the resources which the advances of fifty years had made available. If the surgical problems of modern war can be said not to differ sensibly from the campaigns of the past, the form in which they have been presented is certainly as different as are the methods of their solution. The achievements in the field of discovery of the chemist, the physicist and the biologist have given the military surgeon an advantage in diagnosis and treatment which was denied to his predecessors, and we are able to measure the effects of these advantages when we come to appraise the results which have been attained.

But although we may admit the general truth of these statements, it would be wrong to assume that modern scientific knowledge was, on the outbreak of the war, immediately useful to those to whom the wounded were to be confided. Fixed principles existed in all the sciences auxiliary to the work of the surgeon, but our scientific resources were not immediately available at the outset of the great campaign; scientific work bearing on wound problems had not been arranged in a manner adapted to the requirements—indeed, the requirements were not fully foreseen; the workers in the various fields were isolated, or isolated themselves, pursuing new researches rather than concentrating their powerful forces upon the one great quest.

However brilliant the triumphs of surgery may be —and that they have been of surpassing splendour no one will be found to deny—experiences of the war have already produced a mass of facts sufficient to suggest the complete remodelling of our methods of education and research.

The series of manuals, which it is my pleasant duty to introduce to English readers, consists of translations of the principal volumes of the "Horizon" Collection, which has been appropriately named after the uniform of the French soldier.

The authors, who are all well-known specialists in the subjects which they represent, have given a concise but eminently readable account of the recent acquisitions to the medicine and surgery of war which had hitherto been disseminated in periodical literature.

No higher praise can be given to the Editors than to say that the clearness of exposition characteristic of the French original has not been lost in the rendering into English.

MEDICAL SERIES

The medical volumes which have been translated for this series may be divided into two main groups, the first dealing with certain epidemic diseases, including syphilis, which are most liable to attack soldiers, and the second with various aspects of the neurology of war. The last word on *Typhoid Fever*, hitherto " the greatest scourge of armies in time of war," as it has been truly called, will be found in the monograph by MM. Vincent and Muratet, which contains a full account of recent progress in bacteriology and epidemiology as well as the clinical features of typhoid and paratyphoid fevers. The writers combat a belief in the comparatively harmless nature of paratyphoid and state that in the present war hæmorrhage and perforation have been as frequent in paratyphoid, as in typhoid fever. In their chapter on diagnosis they show that the serum test is of no value in the case of those who have undergone anti-typhoid or anti-paratyphoid vaccination, and that precise information can be gained by blood cultures only. The relative advantages of a restricted and liberal diet are discussed in the chapter on treatment, which also contains a description of serum-therapy and vaccine-therapy and the general management of the patient.

Considerable space is devoted to the important question of the carrier of infection. A special chapter is devoted to the prophylaxis of typhoid fever in the army. The work concludes with a chapter on preventive inoculation, in which its value is conclusively proved by the statistics of all countries in which it has been employed.

MM. Vincent and Muratet have also contributed to the series a work on *Dysentery, Cholera and Typhus* which will be of special interest to those whose duties take them to the Eastern Mediterranean or Mesopotamia. The carrier problem in relation to dysentery and cholera is fully discussed, and special stress is laid on the epidemiological importance of mild or abortive cases of these two diseases.

In their monograph on *The Abnormal Forms of Tetanus*, MM. Courtois-Suffit and Giroux treat of those varieties of the disease in which the spasm is confined to a limited group of muscles, *e.g.* those of the head, or one or more limbs, or of the abdominothoracic muscles. The constitutional symptoms are less severe than in the generalized form of the disease, and the prognosis is more favourable.

The volume by Dr G. Thibierge on *Syphilis in the Army* is intended as a *vade mecum* for medical officers in the army.

Turning now to the works of neurological interest, we have two volumes dealing with lesions of the peripheral nerves by Mme. Atanassio Benisty, who has been for several years assistant to Professor Pierre Marie at La Salpêtrière. The first volume contains an account of the anatomy and physiology of the peripheral nerves, together with the symptomatology of their lesions. The second volume is devoted to the prognosis and treatment of nerve lesions.

The monograph of MM. Babinski and Froment on *Hysteria or Pithiatism and Nervous Disorders of a Reflex Character* next claims attention. In the first part the old conception of hysteria, especially as it was built up by Charcot, is set forth, and is followed by a description of the modern conception of hysteria due to Babinski, who has suggested the substitution of the term "Pithiatism," *i.e.* a state curable by persuasion, for the old name hysteria. The second part deals with nervous disorders of a reflex character, consisting of contractures or paralysis following traumatism, which are frequently found in the neurology of war, and a variety of minor symptoms, such as muscular atrophy, exaggeration of the tendon reflexes, vasomotor, thermal and secretory changes, etc. An important section discusses the future of such men, especially as regards their disposal by medical boards.

An instructive companion volume to the above is to be found in the monograph of MM. Roussy and Lhermitte, which embodies a description of the psychoneuroses met with in war, starting with elementary motor disorders and concluding with the most complex represented by pure psychoses.

SURGICAL SERIES

When the present war began, surgeons, under the influence of the immortal work of Lister, had for more than a quarter of a century concerned themselves almost exclusively with elaborations of technique designed to shorten the time occupied in or to improve the results obtained by the many complex operations that the genius of Lister had rendered possible. The good behaviour of the wound was taken for granted whenever it was made, as it nearly always was, through unbroken skin, and hence the study of the treatment of wounds had become largely restricted to the study of the aseptic variety. Septic wounds were rarely seen, and antiseptic surgery had been almost forgotten. Very few of those who were called upon to treat the wounded in the early autumn of 1914 were familiar with the treatment of grossly septic compound fractures and wounded joints, and none had any wide experience. To these men the conditions of the wounds came as a sinister and disheartening revelation. They were suddenly confronted with a state of affairs, as far as the physical conditions in the wounds were concerned, for which it was necessary to go back a hundred years or more to find a parallel.

Hence the early period of the war was one of earnest search after the correct principles that should be applied to the removal of the unusual difficulties with which surgeons and physicians were faced. It was necessary to discover where and why the treatment that sufficed for affections among the civil population failed when it was applied to military casualties, and then to originate adequate measures for the relief of the latter. For many reasons this was a slow and laborious process, in spite of the multitude of workers and the wealth of scientific resources at their disposal. The ruthlessness of war must necessarily hamper the work of the medical scientist in almost every direction except in that of providing him with an abundance of material upon which to work. It limits the opportunity for deliberate critical observation and comparison that is so essential to the formation of an accurate estimation of values; it often compels work to be done under such high pressure and such unfavourable conditions that it becomes of little value for educative purposes. In all the armies, and on all the fronts, the pressure caused by the unprecedented number of casualties has necessitated rapid evacuation from the front along lines of communication, often of enormous length, and this means the transfer of cases through many hands, with its consequent division of responsibility, loss of continuity of treatment, and absence of prolonged observation by any one individual.

In addition to all this, it must be remembered that in this war the early conditions at the front were so uncertain that it was impossible to establish there the completely equipped scientific institutions for the treatment of the wounded that are now available under more assured circumstances, and that progress was thereby much hampered until definitive treatment could be undertaken at the early stage that is now possible.

But order has been steadily evolved out of chaos, and many things are now being done at the front that would have been deemed impossible not many months ago. As general principles of treatment are established it is found practicable to give effect to them to their full logical extent, and though there are still many obscure points to be elucidated and many methods in use that still call for improvements, it is now safe to say that the position of the art of military medicine and surgery stands upon a sound foundation, and that its future may be regarded with confidence and sanguine expectation.

The views of great authorities who derive their knowledge from extensive first-hand practical experience gained in the field cannot fail to serve as a most valuable asset to the less experienced, and must do much to enable them to derive the utmost value from the experience which will, in time, be theirs. The series covers the whole field of war surgery and medicine, and its predominating note is the exhaustive, practical and up-to-date manner in which it is handled. It is marked throughout not only by a wealth of detail, but by clearness of view and logical sequence of thought. Its study will convince the reader that, great as have been the advances in all departments in the services during this war, the progress made in the medical branch may fairly challenge comparison with that in any other, and that not the least among the services rendered by our great ally, France, to the common cause is this brilliant contribution to our professional knowledge.

A glance at the list of surgical works in the series will show how completely the ground has been covered. Appropriately enough, the series opens with the volume on *The Treatment of Infected Wounds*, by A. Carrel and G. Dehelly. This is a direct product of the war which, in the opinion of many, bids fair to become epoch-making in the treatment of septic wounds. It is peculiar to the war and derived directly from it, and the work upon which it is based is as fine an example of correlated work on the part of the chemist, the bacteriologist and the clinician as could well be wished for. This volume will show many for the first time what a precise and scientific method the " Carrel treatment " really is.

The two volumes by Professor Leriche on *Fractures* contain the practical application of the views of the great Lyons school of surgeons with regard to the treatment of injuries of bones and joints. Supported as they are by an appeal to an abundant clinical experience, they cannot fail to interest English surgeons, and to prove of the greatest value. It is only necessary to say the *Wounds of the Abdomen* are dealt with by Dr Abadie, *Wounds of the Vessels* by Professor Sencert, *Wounds of the Skull* *and Brain* by MM. Chatelin and De Martel, and *Localisation and Extraction of Projectiles* by Professor Ombrédanne and R. Ledoux-Lebard, to prove that the subjects have been allotted to very able and experienced exponents.

ALFRED KEOGH

PREFACE TO THE ENGLISH TRANSLATION

This volume is one of a series of translations published by the University of London Press under the general editorship of Sir Alfred Keogh, G.C.B., Director-General, Medical Services, the translations being from French monographs on military medicine and surgery. I have been asked to help in regard to this particular work on the subject of malaria in Macedonia.

The book evidently gives the personal experiences and studies of the authors in connection with this subject, and will prove of interest and value to all medical men who are called upon to treat malaria, not only from Macedonia but from other parts of the world. But I would advise the reader to study it, if possible, together with other works on malaria. Of course, the literature of malaria, which now extends over two thousand years, is enormous; and the military medical officer is seldom able to obtain easy access even to the most classical books on the subject. Perhaps, however, he can generally obtain volume CL of the New Sydenham Society's translations, containing the classical monographs of Marchiafava and Bignami on Roman malaria, and of Mannaberg on Austrian malaria. If he can do so, he should also consult especially Thayer and

Hewetson's *Malarial Fevers of Baltimore*—not to mention such standard works as Castellani's and Chalmer's *Manual of Tropical Medicine* and Manson's *Tropical Diseases*. Nothnagel's *Encyclopædia of Practical Medicine* (volume on Malaria, Influenza, and Dengue, 1905) contains a more complete monograph by Mannaberg, and volume XIX of *Twentieth Century Practice*, (Sampson Low, Marsden, & Co.) has a more complete article on malaria by Marchiafava and Bignami.

The little book by Drs P. Armand-Delille, P. Abrami, G. Paisseau, and Henri Lemaire scarcely pretends to be a full monograph upon malaria, and, as I said, describes almost entirely the authors' own observations and conclusions. The latter will not always be accepted by those who have studied the disease in many parts of the world and in the light of previous literature. For example, when describing the symptoms, the authors may perhaps be criticised for not having distinguished sufficiently carefully the symptomatology of infections by the different species of parasites, and under quinine or not under quinine. Personally, I think that each species produces different symptoms in accordance with the distinctions given in the older works. In this connection many readers would have preferred that the authors had given more details regarding the comparative frequency of the different syndromes which they actually observed, instead of merely recording that such and such syndromes were found in their cases: obviously the frequency of a given syndrome in a disease is a very important point, especially when we remember that the clinical picture may occasionally be very much blurred by the simultaneous presence of other infections. I doubt whether such a distinction as that which the authors draw between primary paludism and secondary paludism is sufficiently frequent to be stated as a general law. Everyone has known, from the time of the ancients, that the intermittent fevers begin by being remittent; and this phenomenon was fully described and explained by Torti two centuries ago.

Many students of malaria are also likely to disagree with the authors in their acceptance of the speculation of F. Schaudinn, that relapses are due to parthenogenesis in the gametocytes. We frequently find in biological works that what is first put forward by some writer as a mere speculation shortly afterwards becomes a probable hypothesis, and then later becomes a very probable hypothesis, and finally ends by becoming a certainty—and all this without the presentment of any further proof! The said speculation of parthenogenesis was one of the many speculations put forward by Schaudinn on the most slender evidence possible; and though several observers have written since then on the supposed parthenogenetic gametocytes, little further proof of his notion has been adduced. On the other hand, there are very many reasons against the speculation (*vide*, for instance, my book on the *Prevention of Malaria*). Although a large number of cases of Macedonian malaria are now being minutely studied in Britain, we have hitherto failed to find anything approaching verification; and it is a much easier thing to believe that the rallies and relapses so frequently seen in all kinds of malaria are due merely to decrease and increase of the numbers of asexual parasites, depending most probably upon the varying resistance of the host—as in many other diseases. The authors are, of course, fully entitled to their opinion, but the industrious reader should compare their views on the point with those of other writers. The best works are apt to differ on matters of opinion like these.

In his Preface to this book, Professor A. Laveran, whose great discovery of the parasites of malaria was the basis of all modern studies of malaria, criticises another point made by the authors. They teach that when one relapse is over we should suspend the administration of quinine until the following relapse. He does not accept this view; and here again there is much divergence of opinion. The point is really of superlative importance in military medicine, which requires that patients should be permanently cured as soon as possible. Unfortunately experience has shown how difficult it is to do this. Thus, in my own experience, over forty different kinds of treatment, conducted by the best clinicians with the advice of the best pathologists, have hitherto failed to effect an absolute cure with certainty, though, on the other hand, nearly all these treatments are able to reduce the fever and the parasites quickly and with ease, but only temporarily. It is also comparatively easy to prevent the occurrence of relapses by administering something like ten grains of quinine daily, that is, while this administration continues; but, unfortunately, a persistence in this line of treatment even for months does not necessarily cure a patient entirely. Dr Laveran thinks that quinine ought to be continued between the relapses, but a school of clinicians considers that this procedure produces some kind of resistance either in the patient or in his parasites which renders it more difficult to cure relapses when they occur. Researches are now being made upon this point; but up to the present I must confess that I remain in doubt both ways. I should be more in favour of the authors' views if I were convinced that it would be easier to cure relapses when they occur if no quinine at all has been given in the interval, but, unfortunately, I am not convinced of this as yet. I can, however, say definitely that the authors' remark that " quinine treatment carried out during the period of apyrexia with the object of preventing the approaching relapse invariably proves ineffective " does not accord in the least (as I have said) with our experiments made on large bodies of men, which show that while 30 per cent. of men relapse during one month while they are actually taking 5 grains of quinine a day, only about 10 per cent. relapse while they are taking 10 grains or 15 grains a day for the same period. And indeed this remark is contrary to the almost universal experience of clinicians; though, I admit, a very few cases relapse in spite of the most vigorous quinine administration.

Other points with which some persons will disagree are: (1) That defervescence frequently takes place on the sixth or twelfth days from the commencement of the fever; (2) that such things as septan and biseptan rhythms exist; (3) that pernicious attacks are due only to excessive numbers of parasites; (4) that during hæmoglobinuria the blood "is as rich in parasites as during an ague fit"; moreover (5), the hypothesis that double sets of parasites producing double tertian fevers are due to the fact that the patients were originally infected on two successive nights has not yet received any proof at all that I know of, though it is a pleasant speculation, in which I myself have always indulged, and probably originated, as a speculation; (6) then, again, the contention that the Anopheles are very frequently found infected in Macedonia has not always been borne out by somewhat extensive studies which I have seen described, and, indeed, only a small proportion of the Anopheles are generally found infected even in intensely malarious localities; lastly (7), the claim that quinine is more rapidly absorbed from isotonic solutions injected intramuscularly than from other modes of administration will certainly be strongly criticised by many chemists who maintain that this is not the case or that there is very little practical difference. A large number of experiments on these points have now been made under myself, and I really cannot detect any marked difference in the results obtained by oral or intramuscular or intravenous administration respectively, and think that if there is any difference it is so small as to be almost negligible. A number of chemical experiments have also been recorded showing that the elimination of quinine in the urine is apt to be a very fallacious test as an indication of the rapidity or completeness of absorption. The authors say that when an isotonic injection is given the patient feels the effects of quinine intoxication in less than half an hour; but I can say definitely from my own personal experience (and I have taken much quinine) that I can obtain precisely the same result from oral doses, especially if given on an empty stomach or just before meals. Webb has shown that the lethal dose for monkeys is often less in injections than in oral administration; but it is obvious that the rapidity of absorption from the former may be greatly influenced by many causes, such as the blood pressure and the active exercise of the muscles in which the injection is made, besides the degree and the tonicity of the solution. I admit that my previous contention, based entirely upon the former work of chemists, that injections are not likely to be so useful as oral administration, except in special cases, has not been fully supported by recent work; but I still see no reason for supposing that the former is in any way *more* efficacious than the latter. Contrary to some completely misleading statements made in certain quarters, I have never maintained that injections are entirely useless, and have always been willing to advise them where an oral administration is not possible or advisable. Captain Meredith Harrison has recently demonstrated to me that much larger doses of quinine can be well borne by patients if part of these doses is given intramuscularly and the remainder orally.

As this is especially a military work, I have felt it my duty to make these criticisms, not for the purpose of dogmatising in a sense contrary to that of the authors, but simply in order to warn the reader regarding points which appear to me to be doubtful, in the hope that he will study these points for himself, as especially necessary in military practice; and I do not for a moment wish to throw doubt on the value of the work as a whole. On the contrary, I think that the book contains many observations which will not only interest all readers, but which will be found stimulating to them; and I would cite especially the clinical details, which are put in a very modern and thorough manner, and which should be carefully compared by readers with their own observations. The work should be in the hands of everyone called upon to treat malaria.

RONALD ROSS

PREFACE

The epidemic of malaria which attacked the army in the East last summer was no surprise to medical men acquainted with the unhealthy character of the region occupied by our soldiers and the frequency of severe manifestations of the disease in armies in the field.

Endemic malaria, which has always been very frequent in Greece, as the Hippocratic writings testify, is particularly intense in the low and marshy plain which is watered by the Vardar before it empties itself into the Ægean.

The gravity of malaria in armies in the field has been noted by all military epidemiologists, and numerous examples may be quoted which occurred not only in expeditions to hot and unwholesome climates, such as Algeria in the early stages of its conquest, or Madagascar, but also in the history of European wars.

Armies encamped in the plains of the Lower Danube very often suffered from malarial fevers.

During the Turco-Russian War of 1877-8 the Russian army on the Danube had 140,000 cases of malaria and 1092 deaths due to this cause.

In 1828, during the campaign in Morea, and in 1859, during the war with Italy, malaria was extremely prevalent in our army. The French army entered Lombardy in the spring of 1859;

from the beginning of July to the end of September all the diseases became merged in a single one—remittent malarial fever frequently accompanied by a typhoid state.

Even in wars which took place in the north of Europe severe epidemics of malaria were observed.

Pringle relates that the English troops suffered considerably from malarial fevers during the campaign of 1747 and 1748 in the Netherlands.

The landing of the English in the island of Walcheren in August 1808 was followed by one of the severest epidemics of malaria known. From August 28 to December 23 out of an effective of 39,219 men, 4175 died of fevers; from August 21 to November 18 the number of admissions to hospitals, second attacks included, rose to 26,846.

Towards the end of December 1809, after return of the troops to England, there were still 11,503 men suffering from the *Walcheren diseases*. The English army had been beaten before it had done any fighting.[1]

The soldier in the field, who is often obliged to live in unhealthy localities and to pass the night in the open air or under inadequate shelter, is left almost defenceless against the bite of the swarms of *Anopheles*, which inoculate him with large doses of the virus supplied in abundance by the natives or by other soldiers who are already suffering from the disease. Moreover, the soldier is subjected to great fatigue; he has to undertake long marches or to construct trenches in very hot weather, as happened at Salonica, the result being a condition of overwork which diminished his power of resistance to pathogenic agents.

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[1] A. Laveran, *Traité du Paludisme*. 2e édition. Paris, 1907, p. 93.

A few young medical men, who were surprised by the severe and somewhat abnormal forms of malaria observed by them in the army of the East, were of opinion that the pathogenic agent was different from that of the fevers in Europe and Algeria. The examination of the blood of the Salonica patients did not confirm this hypothesis, for it showed the typical forms of the hæmatozoa of malaria, the only remarkable feature being the abundance of the parasite and the predominance of those forms which are least affected by treatment.

In giving to their book the title of " Malaria in Macedonia " the writers did not imply that the malaria of Macedonia was of a special nature, but their obvious intention was merely to indicate that their observations had been made in Macedonia or on patients who had been evacuated from that region.

The reader will find in the present work excellent clinical descriptions and judicious advice as to the treatment of malaria.

One remark, however, is necessary in connection with the treatment advocated by Dr Abrami. In the chapter dealing with the treatment of the first invasion of paludism (treatment of the intervals between the relapses), we find it stated that " when once the relapse is over, *we suspend the administration of quinine* until the following relapse." It is also stated, à propos of the treatment of secondary paludism, that "we have completely abandoned the administration of quinine during the intervals between relapses." Personally I have always maintained that it was not sufficient to cut short the fever, but that an effort should be made to prevent relapses by successive treatments, since if the administration of quinine is suddenly stopped, the parasites which have been temporarily arrested in their development soon come to life again and all has to be begun over again.

I can invoke great authorities to support my view. Even in the seventeenth century Lind and Sydenham had realised the value of successive treatments by quinine in malarial fever. In more modern times Bretonneau and Trousseau have insisted on the necessity of continuing the use of quinine in malaria after the fever had been cut short, so as to avoid relapses.

It is quite true, as the writers of this work state, that the apyretic period following a relapse should be utilised for repairing the losses suffered by the organism, but this reconstructive treatment is not incompatible with a judicious and intermittent use of quinine. On the contrary, the first indication should be to diminish the number of the relapses and to lessen their severity.

The work of Drs Armand-Delille, Abrami, Paisseau, and Lemaire appears opportunely, for in spite of all the prophylactic measures which have been taken it is unfortunately probable that our army of the East will suffer again this summer from malaria and that the medical officers in our hospitals will have to treat a large number of cases evacuated from Salonica. For a long time to come the fevers of Macedonia will be spoken of in France just as the Walcheren diseases used to be in England in days gone by.

A. LAVERAN,
Membre de l'Institut

June 14, 1917

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INTRODUCTION

The outbreak of malaria in Macedonia in the army of the East was one of exceptional severity. Not only did it present all the characters of tropical malaria, but it also assumed a special clinical appearance owing to the fact that it attacked hitherto unaffected subjects, exposed to conditions of fatigue inseparable from every important military campaign.

Fortunately the supply of quinine, which had been laid in opportunely, enabled the preventive and curative treatment to be better organised than in previous colonial campaigns. The severity of this infection, great and extensive as it was, could thus be reduced; though the incidence of the disease among our troops was high the mortality was relatively very low.

Malaria has been studied in a masterly manner by Laveran and Grall and Marchoux, to mention these classical writers only, and reference should always be made to their textbooks. At present, therefore, our object is merely to lay before the medical profession a sketch of the principal clinical features of the disease as we have observed it in the army of the East.

We shall deal, therefore, merely with primary and secondary manifestations of malaria, and we shall study its diagnosis almost exclusively from the standpoint of hæmatology and parasitology. These methods enable a certain diagnosis to be made, and consequently dictate the specific treatment.

The chief interest of this study lies in the fact that our field of observation was formed by a large number of subjects who had never had any previous attack of malaria.

MALARIA IN MACEDONIA

Chapter I

PARASITOLOGY

Malaria is due to the development in the organism of a protozoon discovered by Laveran, which is inoculated by the bite of the Anopheles mosquito, and by the female Anopheles exclusively. This protozoon assumes three very different types, which most parasitologists consider nowadays as three distinct species, the *Plasmodium vivax*, the agent of benign tertian; the *Plasmodium malariæ*, the agent of quartan fever; and the *Plasmodium præcox* or *falciparum*, the agent of tropical fever, æstivo-autumnal fever or malignant tertian.

Although they form distinct species, these three parasites should be grouped together under the generic name of malarial hæmatozoa, because they present similar biological and developmental characters and pathogenic properties, and are affected by the same therapeutical agent, quinine. They can only be inoculated into man by the bite of the female Anopheles, in whose organism they undergo an identical evolution; after being introduced by the saliva of the mosquito they reach and penetrate the red corpuscles and develop in the form of a small amœba, which is first of all round (schizont) and then irregular owing to the pseudopodia protruded from its protoplasm (amœboid body). They increase in size at the expense of the corpuscle which they have invaded. After some time the parasite divides by repeated segmentation of its nucleolus; it then forms a rounded mass, in the centre of which is a collection of pigment, constituted by the union of ten, twelve, or sixteen nucleoli, arranged like rosettes round the centre and each surrounded by a thin zone of protoplasm (*rosette body*). This process of division of the parasites is called *schizogony*. When the rosette body is mature it becomes dissociated. Each of the nucleated elements which constituted it, after being set free by the rupture of the red corpuscle, is discharged as a *merozoite* into the circulating blood, where it fastens upon a red corpuscle, becomes transformed in turn into a schizont, as a merozoite attached to a red corpuscle is called, then into an amœboid body, and finally into a rosette body, the cycle continuing in the same way.

The hæmatozoon also gives rise to certain elements, whose role is all important, known as *gametes* (sexual forms). These elements are formed at the expense of the schizonts and amœboid bodies, which instead of dividing into *rosette bodies* become transformed into a body which is either rounded (in *Plasmodium vivax* and *Plasmodium malariæ*) or falciform (in *Plasmodium falciparum*), and is soon set free in the circulation. This body, which is the *gamete*, possesses two extremely important biological properties. In the first place, it is responsible for the chronicity of malaria in the human organism and, secondly, it is the cause of the persistence of malarial endemics throughout the globe.

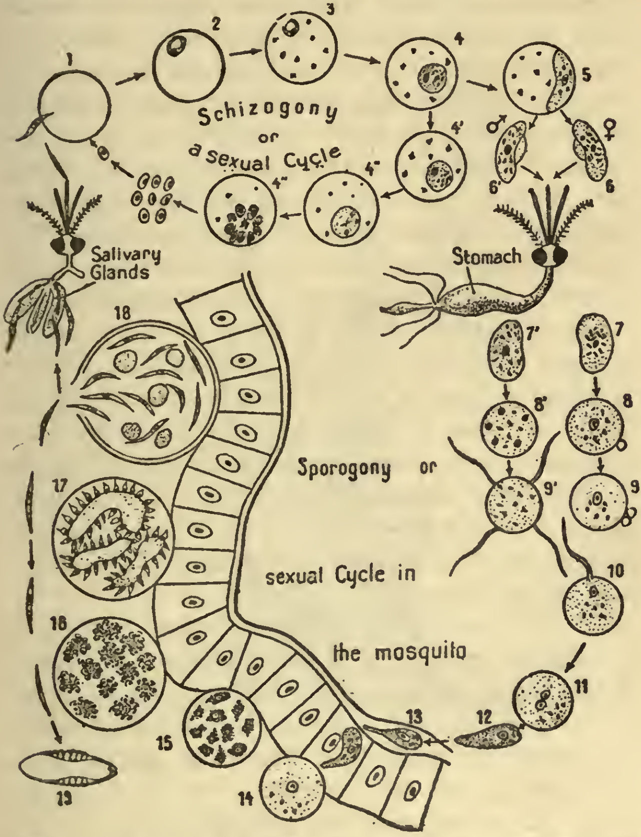

Fig. 1.—Evolution of the *Plasmodium falciparum*. *Est.*, Stomach of the *Anopheles*; *gl. sal.*, salivary glands (after Brumpt). 1, 2, 3. Schizonts. 4. Amœboid body. 4'''. Rosette body. 5, 6. Gametes. 7-11. Fecundation. 12. Zygote. 15-18. Oöcyst.

The *gamete* is extremely resistant to quinine; while the vegetative forms (schizonts, amœboid bodies, and rosette bodies) are destroyed by the drug, the gametes may persist in the organism for months or years. Now under certain conditions when the organic resistance gives way, under the influence of fatigue or meteorological circumstances, the gametes, which had hitherto remained quiescent like parasitic cysts, begin to divide and by multiplication of their nucleus give rise to a rosette body, the rupture of which sets free the merozoites. The latter at once attack the red corpuscles, increase in size and number, and the ordinary cycle of schizogony is reproduced. This special process of segmentation of the gametes is called retrogressive schizogony or "parthenogenesis of the gametes." This is the ordinary process in relapses of malaria. It can easily be understood that as long as these special elements persist in the organism, the patient is exposed to a relapse, and it is in this sense that it may be said that the gamete, and the gamete only, keeps up the chronicity of the disease.

On the other hand, when a female Anopheles has sucked up the blood of a malarial individual, if the blood contains only the vegetative forms of the hæmatozoon (schizonts, amœboid bodies, and rosette bodies), these forms are destroyed in the organism of the mosquito. If, on the contrary, the blood contains gametes, not only do they persist in the body of the Anopheles, but they multiply in it to such an extent that in a short time the salivary glands of the mosquito are invaded by an enormous quantity of parasites, and if it bites a healthy man, it will inevitably inoculate the disease. Without gametes, therefore, there would be no endemic of malaria. The development of the gametes within the Anopheles offers a very peculiar character, which we will describe in a few words. Among the gametes absorbed by the Anopheles in the blood of the malarial individual, some, viz., the *macrogametes*, behave like female elements, while others, viz., the *microgametes* (or *micro-gametocytes*), behave

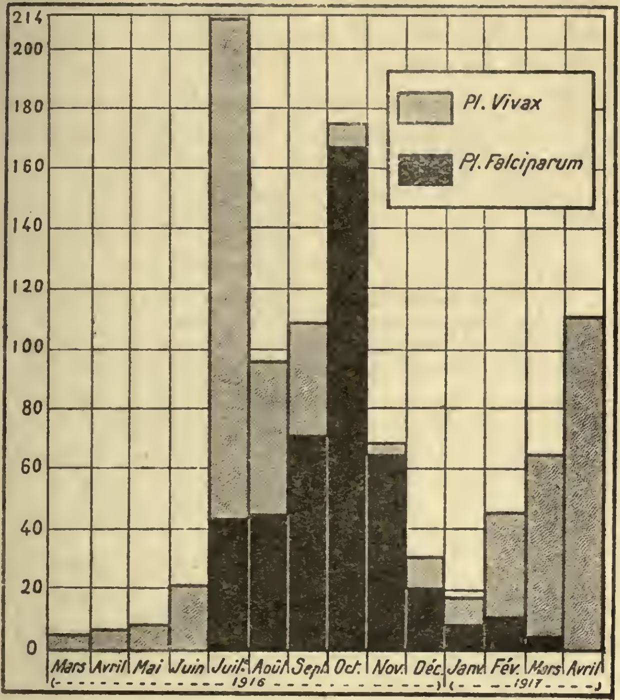

FIG. 2.—Relation of *Pl. vivax* to *Pl. falciparum* observed during the period of a year in the Army Laboratory.

like male elements. The latter protrude at their periphery a series of filaments ending in a swollen free part containing chromatin. These filaments or *flagellated* bodies become separated from the microgametes, and make their way by movements resembling those of spermatozoa towards the macrogamete which one of them succeeds in fecundating. After fecundation, the ovum (*oökinete* or *zygote*) thus formed, becomes an

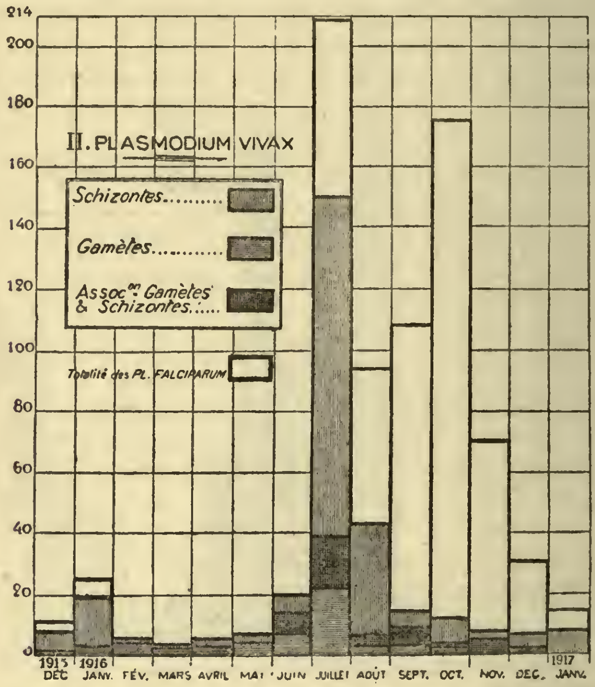

FIG. 3.—Proportion of the different forms of *Pl. vivax* (Army Laboratory).

elongated, mobile element, which passes through the stomach wall of the mosquito and becomes lodged in the muscular coat of the stomach, when it increases in size and becomes surrounded by a resistant zone. It is now an *oöcyst.* This oocyst, which is derived from the fertilized gamete, becomes the seat of an active process of segmentation; its nucleolus, which is primarily single, becomes divided a very large number of times (up to 10,000). A thin band of protoplasm gathers round each of the nucleoli, and the oöcyst is thus filled with 10,000 closely-packed daughter elements, each of which is a *sporozoite.* The oöcyst on reaching maturity ruptures, the sporozoites escape, and reach the salivary glands of the mosquito, the bite of which will inoculate them into human blood.

The hæmatozoon of malaria thus presents two sharply-separated phases, one of sexual life, which takes place solely in the organism of the female Anopheles, the other of asexual life, which occurs in the human organism. In the latter reproduction of the parasite takes place in two ways (1) by schizogony, *i.e.* the formation of rosette bodies at the expense of the adult vegetative forms; (2) by parthenogenesis, or the formation of rosette bodies, at the expense of the unfertilised gametes.[1]

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[1] Hitherto the process has been seen only in the female gametes or macrogametes. P. Armand-Delille, G. Paisseau, and H. Lemaire. *Note sur les constatations positives d'hématozoaires de bactériologie de l'Armée de l'Orient pendant l'année* 1916. *Bull. de la Soc. de Path. exotique.* Meeting held April 11, 1917.

The chapter on *microscopical diagnosis* contains a description of the characters whereby each of the three varieties of the hæmatozoa can be recog-

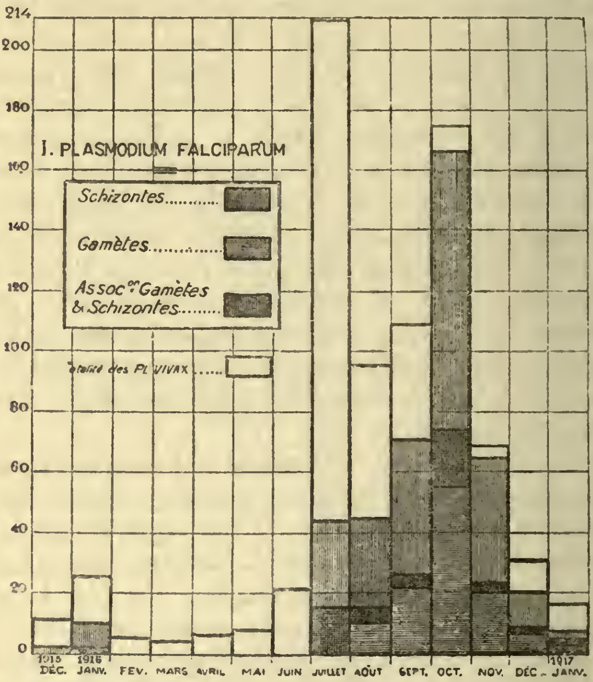

FIG. 4.—Proportion of the different forms of *Pl. falciparum* (Army Laboratory).

nized in the blood of the patient in their various stages of development.

It seems important to mention here that of these three parasites the *Plasmodium malariæ*, the agent of quartan fever, is absolutely exceptional in Macedonia, where investigations made in different laboratories have shown it to be present in only ten cases; the *Plasmodium falciparum*, the agent of tropical fever, represents in summer (July-November) more than 85 per cent. of the cases of malaria; while the *Plasmodium vivax*, the agent of benign tertian, is rare in summer, occurring in only 15-17 per cent., and becomes very predominant from December to July.

The overwhelming majority of mosquitoes in Macedonia consist of the *Anopheles maculipennis* or *claviger*; *A. bifurcatus*, *Pyretophorus superpictus* and *Myzorhynchus pseudopictus* have been caught much less frequently. The quantity of Anopheles reaches absolutely extraordinary proportions in some regions of Macedonia, it being possible to catch hundreds of dangerous mosquitoes in a few hours.

This enormous number of Anopheles, to which Niclot, the principal medical officer, has drawn attention, possesses special interest. It is this factor which to a great extent accounts for the severity of malaria in Macedonia. In a country where there are innumerable carriers of the virus, both in the civil population and among the troops, a very large number of Anopheles are infected.

The result is that men are exposed to inoculations of the malarial virus several times a day, and this accumulation of repeated doses gives rise to a disease which is at once more severe and more resistant to quinine. Permanent and ubiquitous reservoirs of the virus, an exceptionally large quantity of the Anopheles, and the malignant nature of the parasite inoculated (*Plasmodium* *falciparum*), represent the three principal factors of gravity in a malarial endemic in Macedonia. Deterioration of the inoculated subject, which is a necessary consequence of the conditions imposed on the troops as the result of war, is naturally to be added to the factors already mentioned.

Chapter II

CLINICAL STUDY

During the first months of its course in a hitherto unaffected subject, malaria is not manifested by tertian, quartan, or quotidian intermittent paroxysms, but by febrile attacks of very different types, which constitute as a whole *primary paludism.* This is clearly brought out in some textbooks on tropical medicine, especially that by Grall. We shall describe successively :—

1. A *primary paludism,* which dates from the time of infection until the appearance of the intermittent paroxysms.

2. A *secondary paludism,* characterized by frank intermittent and well-disciplined attacks, which we have chiefly observed in winter and the beginning of spring.

Primary paludism includes several phases. The first phase is called the *invasion,* which commences ten to fifteen days after inoculation, during which the patient usually presents a febrile syndrome of relatively short duration.

Then, as a rule, there occurs *a period of apyrexia,* of variable duration, during which the patient appears to have recovered. But the recovery is only apparent, as the patient for several months will present a series of febrile attacks of various types, which constitute as a whole the *second phase*, or *phase of relapses and second attacks*.

This in turn is succeeded by secondary paludism, in which, in addition to frank intermittent attacks, we shall describe certain manifestations which only occur in the subjects of prolonged malarial intoxication.

In addition to malaria of normal evolution we shall have to describe masked and incomplete forms. It is obvious that in this short study, and even in a more didactic description, a certain number of atypical and abnormal forms liable to be met with in practice will have to be passed over.

These are the cases which can only be identified by hæmatological examination.

CHAPTER III

SYNDROMES OF THE FIRST INVASION OF PRIMARY PALUDISM

THE phenomena characterizing the period of the first invasion of primary paludism generally assume the clinical appearance of *febrile gastric derangement.* This is the syndrome which we have observed in subjects who have recently landed; it sometimes occurs less than three weeks after their arrival in the malarial region. It is also by far the commonest manifestation of malaria at the onset of an epidemic in the second part of June; that is to say, in the month following the hatching of the female Anopheles. This febrile gastric derangement may assume a severe form, simulating typhoid fever, or, on the contrary, remain very slight and only be manifested by what is generally known as a feverish attack.

1. SYNDROME OF FEBRILE GASTRIC DERANGEMENT

During a short prodromal period of three or four days before presenting any fever, the patient suffers from vague malaise, headache, and a feeling of muscular fatigue, and the appetite is lost. He generally attributes these symptoms to the heat or to overwork. Often even he does not pay any attention to them, and the affection appears to start suddenly with slight shivering, a rise of temperature, or a sensation of heat. The patient then complains of severe aching in all his limbs and of lumbar and epigastric pain. The headache begins in the morning and gets worse towards the

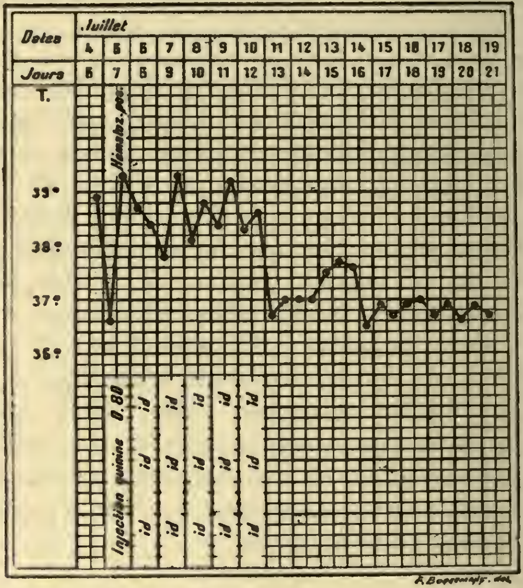

FIG. 5.—Febrile gastric derangement of the first invasion (Dr Abrami).

evening. There is absolute anorexia, the tongue is dirty and coated, vertigo and nausea are constant, and vomiting is frequent. Constipation is the rule, but sometimes a little diarrhœa of indefinite character may be noted.

Nothing definite is found on examination of the various organs; the respiratory system is normal, the abdomen is not distended or tender, and the liver is not enlarged, but the spleen is undoubtedly increased in size. The splenomegaly, however, is slight, similar to that found in typhoid fever. By hooking the fingers under the left costal margin it is often possible to feel the lower pole of the organ, which is tender on pressure. The patient also complains of a painful dragging or stitch in the splenic region. The temperature reaches 100·4° F. on the first day, and for three, four, or even five days keeps at a level of 101·2° or 102·2°, usually with oscillations of not more than a degree. Defervescence takes place, as a rule, by lysis in two or three days at most, even without the administration of quinine, and occurs without any of the ordinary critical phenomena of the ague fit.

If the temperature be taken every hour it will be found that the daily acme takes place at the beginning of the afternoon. The pulse follows an almost parallel path with that of the fever, but increases a little more rapidly in the course of the day.

It can readily be understood that with symptoms of this kind the nature of the affection is often unrecognized, and is regarded as a mere febrile gastric derangement, a paratyphoid fever, or a typhoid fever attenuated by vaccination.

The difficulty may be further increased owing to the co-existence of an affection which is also prevalent in summer in Macedonia, viz., *Mediterranean dengue*, or three day fever.[1]

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[1] *Vide* Sarrailhé, Armand-Delille, and Ch. Richet fils, *La dengue*

But the more sudden onset, intensity of the prostration, cervical and lumbar rachialgia, pains in the bones of the limbs, rapidity of course, absence of vomiting and splenomegaly, and occasionally the characteristic eruption are diagnostic features, in addition to the profound asthenia met with in convalescence, which is surprising in so short a disease.

The patient leaves hospital apparently cured, but if he has not been given sufficient quinine, he will shortly afterwards show clinical manifestations characteristic of the disease.

2. MALARIAL CONTINUED FEVER OF TYPHOID CHARACTER

The continued fever of the first invasion may assume a typhoid form. After a few days' malaise, the patient suddenly feels that his condition is getting worse; he is seized with shivering, intense fever, headache, generalized aching, and lumbar and epigastric pain. He is in a state of profound asthenia, exhausted and prostrate; his sleep is restless and interrupted occasionally by mild delirium. He has frequent mucous vomiting, a constant state of nausea, a thickly-coated tongue, and slight epistaxis.

méditerranéenne ou fièvre de trois jours. C. R. Acad. de Méd., Oct. 1915.

Sarrailhé, *Dengue et fièvre de trois jours. Bull. de la Soc. de Path. exotique*, Dec. 13, 1916.

Armand-Delille, *Notes sur les principaux caractères de la dengue méditerranéenne. Bull. Soc. Méd. des Hôp.*, Nov. 1916.

On examination it will be found that there is little involvement of the thoracic or abdominal organs. The abdomen is not distended or retracted, and diarrhœa is exceptional; the liver, however, reaches a little below the false ribs, and is slightly tender on pressure; the spleen undergoes some hypertrophy, which somewhat exceeds that found in typhoid fever. It is on a level with the costal margin, and is tender on palpation. The patient complains spontaneously of a stitch or a feeling of weight in the left hypochondrium. Examination of the respiratory organs is completely negative. The urine as a rule contains no albumin, and has merely the character of all febrile urine.

The pulse is quickened and very compressible, the arterial tension being definitely lowered. Its frequency is parallel with the temperature. The fever, which at the very first had risen to 103·2° or even 104·8°, keeps at this high level for a fortnight or even three weeks. On taking the temperature hourly it will be found that it begins to rise in the morning, reaches its acme at the beginning of the afternoon, and falls to the lowest level in the first part of the night.

The temperature curve regularly presents two breaks or relative defervescences, one on the fifth or sixth day, and the other on the eleventh or twelfth day. In moderate cases defervescence is sudden and final on the twelfth day; in serious cases a recrudescence takes place, and the course of the fever becomes prolonged, lasting even for a third week.

Frequently, even in the severest forms, the continued fever gives way to a series of quotidian attacks, with large oscillations, of which the lowest

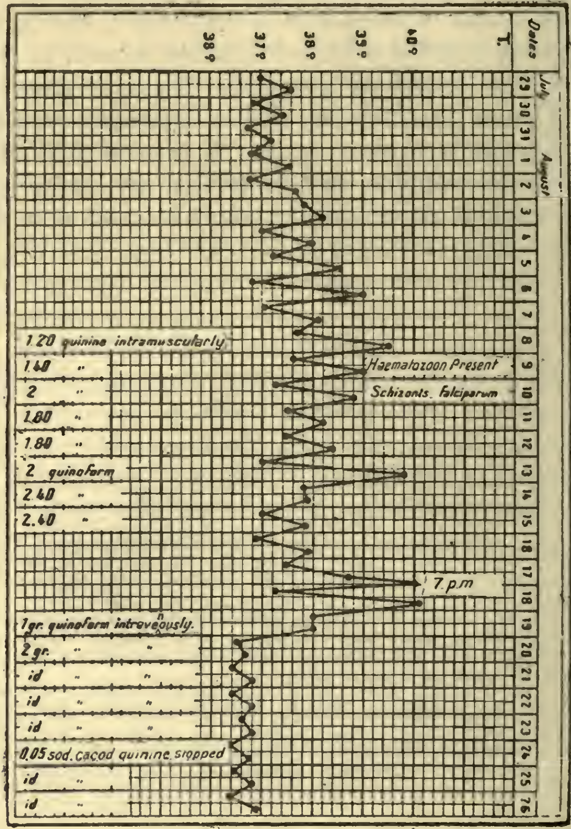


FIG. 6.—Continued malarial fever with a typhoid course (Dr Gassin).

readings are about 99·2° and the highest above 104·0° F. This daily intermittent fever lasts for some days, and is followed by a definitive fall of temperature.

The typhoid form of the first invasion of paludism might easily be confounded with a true typhoid fever, but the rarity of abdominal symptoms, the absence of any pulmonary manifestations, and the special temperature chart are sufficient to enable the medical man who is on his guard to make a correct diagnosis, which will be confirmed by a negative typhoid blood-culture and a positive result as regards the hæmatozoon. This severe form of malarial continued fever occurs among subjects who are profoundly infected by the *Plasmodium falciparum*, their blood being rich in small annular schizonts.

3. ATTENUATED FORM OF INVASION, FEBRILE MALAISE, AND FATIGUE

The symptoms of the first invasion may be much more insidious than in the two forms just described. The patient is not obliged to take to bed; for a period, which is usually fairly short, but which may vary from four to six days, he merely has a feeling of abnormal fatigue and asthenia, which he attributes to the summer heat, for the epidemic is always at its worst in the hot season.

In addition to his unusual sense of fatigue, which chiefly occurs in the early hours of the afternoon, and is accompanied by somnolence, there is considerable digestive disturbance, anorexia, and a state of nausea. The patient also suffers from headache, which is increased by the slightest physical or intellectual effort, and often shows a daily exacerbation about midday. Lastly, in contrast with the somnolence during the day, there is insomnia at night. If the patient is a careful observer, he will notice transient febrile attacks, characterized by slight shivering, accompanied by short spells of heat and then of slight perspiration. The malaise is almost always followed by a feeling of well-being at the end of the day. The symptoms are sometimes sufficiently pronounced to necessitate temporary exemption from military duties, but often they are so slight that they escape notice.

The three syndromes which we have just described are much the most usual form of continued fever of the first invasion of malaria. Patients, however, are sometimes seen who are suffering from malaria, though their fever is of an entirely different character, viz., a fever of intermittent type accompanied by the same symptoms of gastric derangement. The fever shows great oscillations, the lowest temperatures being about 98·6°, and the highest sometimes exceeding 104° F. The attacks recur daily, constituting *quotidian intermittent fever*. The patient complains of intense headache, insomnia, pains in the limbs, and lumbo-epigastric pain. He is depressed and asthenic. His tongue is dirty; he suffers from nausea, and there is frequent vomiting of mucus. The symptoms show an exacerbation at the time of daily rise of temperature.

But, according to the opinion of numerous writers, this quotidian intermittent fever is only apparently a manifestation of the first invasion, since on careful inquiry it will always be found that the patient had previously suffered from malaria or a febrile attack, constituting the true stage of invasion which had escaped notice.

CHAPTER IV

PERIOD OF RELAPSES AND SECOND ATTACKS IN PRIMARY PALUDISM

AFTER the termination of the period of invasion, malaria enters into a silent phase in which the patient appears cured, even if he has been insufficiently treated; this period sometimes lasts from two to four weeks, rarely longer. Most of the patients return to their depôt; they may even have rejoined their unit when they again develop symptoms which may assume a considerable gravity. These symptoms are due to a relapse, or second attack of paludism. In the case of relapse there is no fresh infection, but the patient's organism has not been sterilized by the treatment; he remains a gamete carrier, and a renewed growth of the parasites takes place of varying periodicity and intensity, giving rise to fresh manifestations of the disease.

In the case of a second attack, the subject who has remained in an infected country and exposed to contagion contracts successive and frequently intense reinfections. He then presents fresh malarial manifestations, which are generally severe.

Some writers have wanted to make a distinction between a relapse and a second attack, based on clinical grounds.

As regards malaria in Macedonia, it appears to us to be impossible to establish such a distinction which, it may be said, possesses no practical importance, as the treatment should be the same in both conditions.

The symptoms which indicate relapses and second attacks do not merely present the character of general infection peculiar to the syndromes of the first invasion. The viscera are more profoundly affected, and some especially so, viz., the hæmatopoietic organs (spleen and bone marrow), the liver, alimentary canal, and suprarenal capsules. The other systems, such as the respiratory, circulatory, and nervous systems, may be involved to some extent.

The disease may assume different clinical forms as the result of the multiple localizations of the infection and their various combinations.

Sometimes the febrile manifestations predominate, giving rise to a general disease of a typhoid character. In other cases, on the contrary, the visceral symptoms become most prominent, and the patient seems to be suffering from an acute visceral affection.

Under certain conditions the general infection is so intense and violent that it causes profound changes in certain essential organs, and gives rise to a dramatic syndrome called the *pernicious attack.*

But, fortunately, malaria does not always show such pronounced symptoms, and its evolution is not always so serious. It may only be revealed by attenuated symptoms of infection, or very slight febrile attacks, when it is known as *defaced paludism.*

The fever may even escape notice, and only localized lesions indicating an organic affection are observed. This constitutes *masked paludism.*

For the sake of clearness, we shall begin by describing the principal types of the temperature curve, and we shall then study the visceral syndromes, pernicious attacks, defaced paludism and masked paludism.

1. THE TEMPERATURE CURVE IN THE PERIOD OF RELAPSES AND SECOND ATTACKS

On reaching the period of relapses and second attacks after the silent phase, in which he might be supposed to be cured, the patient will present a series of febrile attacks of different types, and various forms of fever may be found in the same subject, either succeeding one another immediately without an interval of apyrexia, or separated by an afebrile period of varying duration.

The types of fever which we have most frequently observed are the following :—

(1) Remittent continued fever.

(2) Quotidian intermittent fever.

(3) Tertian attacks of a somewhat special character.

(4) An apparently irregular fever impossible to classify.

(1) **Remittent continued fever** is of the same type as that usually found in the period of invasion and which we have already described. In this form, in which the temperature keeps at a high level, with very slight oscillations, the daily

remissions being inconsiderable, the curve frequently presents two typical breaks towards the

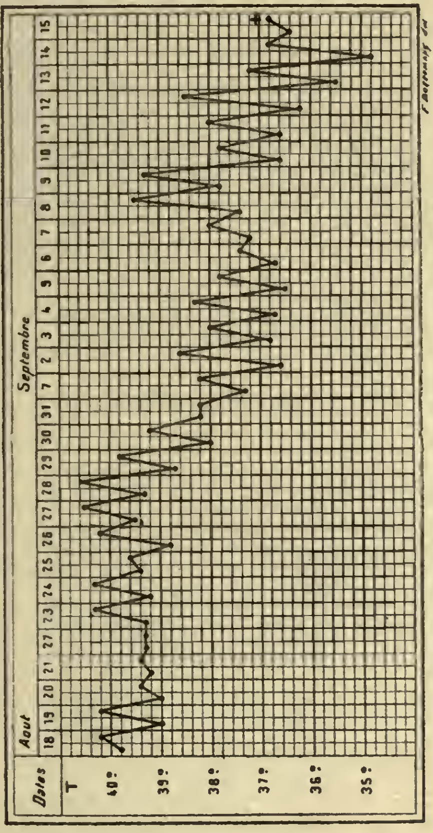


FIG. 7.—Remittent continued fever, ending in cachexia.

sixth and twelfth days, revealed by a defervescence which sometimes lasts less then twenty-four hours.

This continued fever is generally established by some ascending oscillations and the final fall of

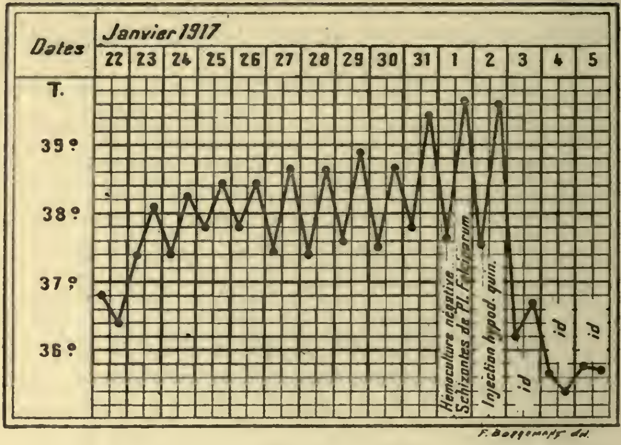


FIG. 8.—Remittent continued fever.

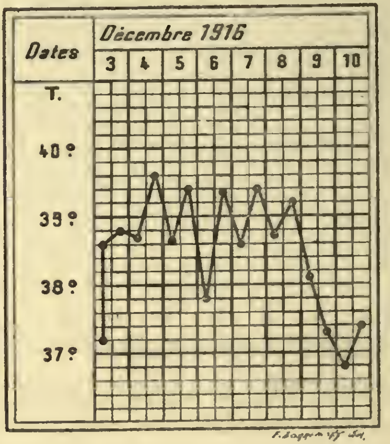
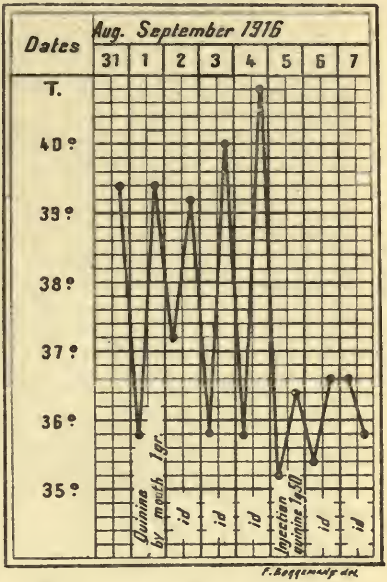


FIG. 9.—Mild remittent continued fever.

temperature, which occurs at the end of the first, second, or third week, usually takes place by lysis.

(2) **Quotidian intermittent fever** is manifested by quotidian attacks with large oscillations recurring for several consecutive days; the rise of temperature begins in the morning; at noon the maximum temperature is reached, *e.g.* 102·2°, 104°, and even 105·8° F., and keeps at this level for some hours. Defervescence begins towards the end of the evening, but is never complete, and the thermometer generally remains above 99·4° F. Quotidian intermittent fever often begins suddenly, with a rise to 104° F.



F. Boggemann del.

FIG. 10.—Quotidian intermittent.

(3) **Isolated attacks** occur in the midst of a phase of more or less complete apyrexia. The temperature, which in the morning was often below 98·6° reaches 104° in the first part of the afternoon, and the next morning defervescence is complete. The temperature may be even subnormal.

(4) **Attacks with a tertian grouping.**—The

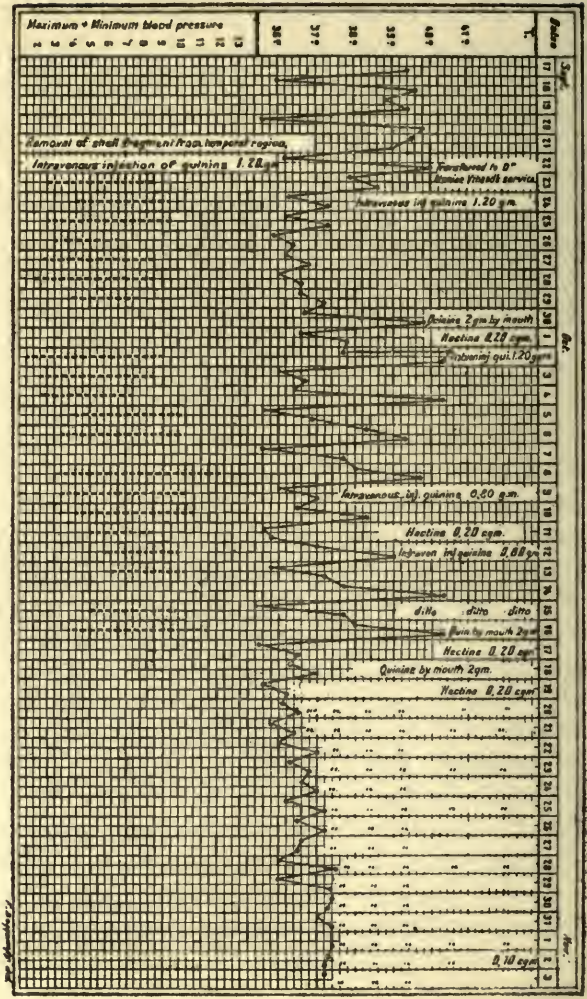


Fig. 11.—Attacks with a tertian grouping.

attacks of fever may be so grouped as to give the chart the appearance of a *fever of the tertian type.* The temperature curve, in fact, seems to be formed by a series of attacks, separated by a day of apyrexia. But on closer examination it will be seen that the apyrexia does not last thirty-six or even twenty-four hours, as in the tertian fever of the secondary period of paludism. It is much shorter, and barely twelve hours after defervescence the fever returns, the reascent is rapidly progressive, and the maximum temperature is reached thirty-six hours after the minimum and forty-eight after the previous maximum.

(5) **Irregular fever.**—Lastly, in some cases the temperature curve has an *irregular character*, which it seems impossible to analyse or classify. As a matter of fact these are often examples of quotidian attacks which are not registered on the chart because the maximum temperatures occur at a very different time from that at which the temperature is usually taken.

These different types of fever may succeed one another without an interval of apyrexia; thus a remittent continued fever is often seen to be followed immediately by a quotidian intermittent. But as a rule the febrile attacks are separated by a phase of apyrexia of very variable duration. In most cases the apyrexial periods are of unequal length, so that no periodicity in the return of the febrile attacks can be detected; in a large number of cases, however, a relative periodicity may be observed. This generally happens in the case of attacks occurring singly or in pairs every six or seven days, or every twelve or fourteen days. This is known as the septan or bi-septan rhythm; the attack may even abort in the second week, and the apyretic period may then last nearly a month.

The temperature curve between the attacks does not always have the same appearance. After the attack it is not uncommon to find a slight hypothermia, the temperature being about 96·8°, and then in the days preceding the following attack it rises a degree. The apyrexial phase, therefore, seems to consist of two stages, the first being one of hypothermia, which follows defervescence from a febrile attack, and the second one, in which the temperature oscillates about 98·6° and heralds a new attack.

2. Syndromes of Visceral Localizations

These clinical syndromes, though they may vary in their localizations, have always a certain number of features in common, viz., anæmia and splenomegaly on the one hand, and asthenia and headache on the other. These symptoms constitute a minimum syndrome, which possesses considerable value in the diagnosis of the nature of a malarial phenomenon. We shall begin this section with a description of anæmia, and will then describe the gastro-bilious, suprarenal, intestinal, cachectic, pulmonary, cardio-vascular and nervous syndromes.[1]

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[1] The reader must not be surprised if he does not find in these pages the redundant and confusing terminology used by most writers. We have adopted, for the sake of clearness, much simpler terms which have nevertheless appeared to us to correspond to the conceptions of contemporary pathology.

ANÆMIC SYNDROMES

Anæmia.—Anæmia [1] is the almost inevitable consequence of malarial infection, and is an early symptom of it; it occurs, indeed, shortly after the end of the period of invasion, at the time of the first relapse of primary paludism. When the anæmia appears, the patient rapidly assumes the special facies which indicates its nature. The face has an earthy pallor, with a dirty yellow tint most marked on the alæ nasi, ears, and labial commissures; the conjunctivæ become subicteric, and pigment patches appear on the forehead and temples resembling the chloasma of pregnancy. An earthy complexion, however, is not seen in all anæmic subjects. Some are only pale or sallow, and their skin and mucous membranes have merely lost their normal colour.

The anæmic process, once established, regularly progresses, and the clinical picture soon becomes complete. The pallor is accompanied by loss of flesh which is usually considerable, and is a special symptom differentiating malarial anæmia from a large number of other anæmic states. The patients also complain of a diminution of their physical strength, of inability to work, and pronounced asthenia; breathlessness on exertion is fairly common; digestive disturbances in the form of anorexia and attacks of diarrhœa are frequent. There is also occasionally slight epistaxis and a little transient œdema over the malleoli.

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[1] *L'anémie du paludisme primaire.* G. Paisseau and H. Lemaire. *Bull. Soc. Méd. Hôp.*, June 1, 1917.

Further examination of the patient will show enlargement of the spleen, which is generally of slight degree, its lower border being on a level with the costal margin or reaching two fingers' breadths below it. The organ is tender on pressure.

The existence of extra-cardiac and anæmic murmurs in the vessels of the neck is also met with; the pulse is of decidedly low tension, exceptionally albuminuria is found, but it is always slight and transient. The anæmia continues to progress, and will increase unless quinine be administered. On the other hand, under the influence of a properly conducted course of quinine the anæmia may subside, the splenic enlargement diminish, the patient regain his weight, and his general condition improve.

Anæmia in primary paludism is not always so pronounced as we have just described it; it may even be so slight that it does not attract the practitioner's attention. In such cases it is only revealed by examination of the blood.

Anæmia in the malarial subject may assume special clinical features owing to the importance of certain symptoms accompanying it; thus we find descriptions of anæmia with hydræmia, hæmorrhagic anæmia, splenomegalic anæmia, and anæmia with icterus.

Anæmia with hydræmia.—Anæmia in malaria is often accompanied by œdema, which, as a rule, is slight and confined to the malleoli and eyelids, but it is not uncommonly seen invading the lower limbs, and even the scrotum, in which case there is considerable puffiness of the face. In exceptional cases the œdema is accompanied by albuminuria, which is always very slight and transient. The duration of the œdema is fairly short, it diminishes in a week or a fortnight, and the hydræmia becomes an ordinary anæmia. The action of diuretics like theobromine and a chloride-free diet is nil, and does not appear in any way to accelerate the absorption of the œdema.

Hæmorrhagic anæmia.—A malarial patient with anæmia very often shows some tendency to hæmorrhages, which may, however, consist of only very slight epistaxis. But if the condition gets worse, it is not uncommon to see the hæmorrhages increase in number.[1]

Sometimes the anæmia is accompanied merely by purpura consisting of petechiæ or of ecchymoses covering the lower limbs and trunk.

In other cases various hæmorrhages are associated with this purpura, constituting a hæmorrhagic purpura, in which the patient presents obstinate epistaxis requiring plugging, hæmorrhage from the gums, hæmaturia, melæna and hæmatemesis, while hypodermic injections give rise to hæmatomata.

The anæmia is aggravated by the hæmorrhagic process, and some patients continue to bleed and die from loss of blood.

Such cases present all the clinical appearances of *progressive pernicious anœmia*, viz., a sallow skin, pallor of the mucous membranes, slight œdema of the lower limbs, multiple hæmorrhages, digestive disturbances, anorexia, vomiting, and diarrhœa.

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[1] *Syndromes hémorragiques dans le paludisme.* G. Paisseau and H. Lemaire. *Bull. Soc. Méd. Hôp.,* Oct. 20, 1916.

In connection with this hæmorrhagic anæmia two points are worthy of attention. The first is the early date of its appearance, which takes place at the very onset of the period of relapses. Hæmorrhagic anæmia is most frequent in the months of July and August; later on malarial anæmia loses this hæmorrhagic character. Secondly, judicious administration of quinine causes a definite improvement in this tendency to hæmorrhages, though urgent cases may require hæmostatic treatment, such as the injection of a few c.c. of horse-serum.

Splenomegalic anæmia.—In some anæmic patients there is considerable enlargement of the spleen, which may form a veritable abdominal tumour reaching down to the umbilicus or the lumbar region, and with a longitudinal dulness of more than thirty centimetres. The enlargement of the spleen develops rapidly, and can be made to subside under the influence of quinine treatment, but the organ is slow in resuming its normal size. There is no other clinical feature characteristic of this form of malarial anæmia, and the examination of the other lymphoid organs always remains negative.

Anæmia with icterus.—We have seen that a malarial patient with anæmia often has subicterus of the conjunctivæ which is of very slight degree, and only accompanied by abnormal pigment in the urine. But it not unfrequently happens in the course of anæmia for attacks of real jaundice to occur, in which the patient's complexion becomes definitely yellow, and the urine contains normal pigment; the stools then assume the polycholic character. The attack of jaundice, which is always of short duration, coincides with an aggravation of the anæmia, or succeeds it. We shall see later that this phenomenon is often a prelude to acute primary cachexia.

Examination of the blood.—The chief hæmatological features of the anæmia of primary paludism can be easily described.

Malarial anæmia presents every degree of severity: the number of the red cells may sometimes fall in severe cases below a million. The loss of the red cells may be very rapid, as the patient in the course of an attack may lose more than a million in a few days.

There is considerable inequality in the size of the red cells and a tendency to increase in their diameter.

Malarial anæmia does not belong to the group of chloro-anæmia, the diminution in the amount of the hæmoglobin not exceeding that of the number of the red cells.

There is generally a diminution in the number of the white cells, constituting leucopenia. Instead of 7500 to 9000 leucocytes, the numbers fall below 6000 and even 3000. Any increase in the number of the leucocytes is very transitory, or is confined to an abnormal form of cell.

The leucocytic formula shows a relative increase of the mononuclears, and therefore a diminution of the polymorphonuclears. The polymorphonuclear count, instead of ranging between 60 and 75 per cent., as it does normally, falls to 50 and even 30 per cent., while the mononuclear count rises and even exceeds 40 per cent.

In severe cases, as soon as the number of the red cells falls to half the normal figure, elements of the bone marrow appear in the blood, viz., granular myelocytes, and even younger cells still, agranular myelocytes. Nucleated red corpuscles are exceptional or in very small numbers, even in the severest cases.

Textbooks state that the blood in malaria contains melaniferous leucocytes, *i.e.* large mononuclears stuffed full of malarial pigment. As a matter of fact these cells are very rare in the circulating blood in the anæmia of acute paludism. They are more frequent in secondary paludism. The presence of all these hæmatological characters constitutes an excellent diagnostic guide to the malarial character of an anæmia, though it does not possess the same value as the discovery of the parasite.

GASTRO-HEPATIC SYNDROMES

Gastro-bilious forms.—The febrile manifestations of the second phase of primary paludism are very frequently accompanied by gastric and bilious syndromes, which usually appear early.

The symptoms at first consist of very severe headache, anorexia, frequent bilious vomiting, and fairly profuse diarrhœa. The patient rapidly develops subicterus of the conjunctivæ and even of the skin, but his urine does not contain bile pigment. Not only does he complain of lumbar and epigastric pain, but also of profound asthenia, with an intense feeling of fatigue. Examination of the patient furnishes more information than at the period of the first invasion. Digestive disturbance is shown by a coated though moist tongue and slight distension of the abdomen, which may be tender on palpation. The liver reaches slightly below the costal margin. The spleen is also enlarged, and to a greater extent than in typhoid fever, sometimes being one to two fingers' breadths below the false ribs, and palpation of the two organs exaggerates the spontaneous pain. The lungs are still unaffected. The heart sounds are normal, but the pulse shows an acceleration corresponding to the rise of temperature and is very compressible; the arterial tension is low, especially the minimum pressure.

This gastro-hepatic syndrome is generally accompanied by a continued fever, but the temperature curve often shows certain peculiarities. It may be immediately preceded by a quotidian intermittent of five or six days' duration; defervescence takes place by lysis, in two or three quotidian attacks, which become progressively less severe.

In grave cases prostration and adynamia dominate the scene, and the temperature, which throughout has been of the continued type, rises progressively, and the patient dies with hyperpyrexia.

In mild and moderate cases defervescence is accompanied by improvement in all the general symptoms.

Form of infective icterus.—In this form also the temperature curve consists of a succession of a continued fever and of a quotidian intermittent.

The onset is violent; the temperature rises suddenly to 104° F., the patient from the first is prostrated and plunged into a condition of profound asthenia. This state of pronounced adynamia is interrupted by mild delirium. Jaundice develops early, and rapidly becomes darker, and the urine contains bile pigment. The jaundice is accompanied by bilious vomiting and greenish polycholic diarrhœa. Hæmorrhages frequently occur, such as epistaxis, bleeding from the gums, purpura, and even hæmaturia and melæna. The tongue is first dirty and then becomes dry and shrivelled; the abdomen is distended and tender, the face drawn and pinched, the pulse weak and very compressible. The liver is two or three fingers' breadths below the false ribs, the spleen is as much enlarged if not more, and both organs are tender on palpation. Signs of congestion are found at the base of the right lung. When the general condition gets worse, the adynamia becomes pronounced, the patient grows livid, and dies from cardio-vascular collapse with an imperceptible pulse and a subnormal temperature. The clinical picture resembles, in short, that of a severe icterus, but the termination is not always fatal, as this form of icterus may end in recovery by a process resembling that of any severe icterus.

This severe form of infective icterus is, however, far from being the most frequent type. During the period of a malarial epidemic an icterus of a mild type is much more frequently observed. This icterus appears rapidly after a short prodromal stage of gastric derangement, and is accompanied by fever, which may assume the continued or the quotidian intermittent type, or occur in the form of isolated attacks. The fever is always of short duration, and the icterus usually does not appear till the time of defervescence. The icterus has all the characters of a choluric icterus, without retention and of mild course; even when there is definite icterus the stools are not colourless, but rather pleiochromic, at least during the first few days. Examination of the organs shows slight enlargement of the liver and spleen. Splenomegaly here possesses great semeiological value, as it presents the characters of the splenic enlargement usually seen in the period of acute paludism, viz., moderate splenomegaly, in which the lower pole of the organ reaches below the costal margin and accompanied by a feeling of weight and sometimes pain in the left hypochondrium. This splenic enlargement suggests that this icterus is of a malarial character, and this suspicion will be confirmed by the negative result of an early blood-culture for typhoid bacilli and by the presence of hæmatozoa in the blood.[1]

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[1] Contrary to the opinion once held it has been established nowadays that acute hepatitis and abscess of the liver are due to the amœba of dysentery, and these phenomena may naturally occur among malarial patients.

SYNDROME OF ACUTE AND SUB-ACUTE SUPRARENAL INSUFFICIENCY[1]

This syndrome may occur in persons whose infection is only a few weeks old. The manifestations have generally been ill-marked, and merely consist of malaise, headache, and a few febrile attacks, so that the patients keep on duty, although they become very anæmic.

Then all of a sudden a violent attack takes place, the temperature rises to 104° F. or higher, and then falls sometimes below normal to 96·8°. The attack is accompanied from the first by digestive disturbances, repeated vomiting and profuse diarrhœa. The patient complains of violent pain localized in the lumbar and epigastric regions. All these symptoms outlive the fall of the temperature and may persist till the end.

On examination of the patient the most striking thing is his state of anæmia and emaciation; his look is profoundly altered, the features are drawn, the nose pinched, the eyes hollow, and the voice hoarse. The vomiting and diarrhœa continue, no fluid is tolerated, and there is almost absolute anorexia. The lumbar pains persist, and the patient suffers from cramps. Asthenia is the principal symptom. The patient retains his lucidity, but is motionless and in such a state of prostration that he requires an orderly to feed him, and he is incapable of sitting without support on his bed, but falls back almost lifeless; the pulse is relatively quickened

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[1] G. Paisseau and H. Lemaire. *L'insuffisance surrénale dans le paludisme. Presse médicale,* Dec. 4, 1916.

(100-110), remarkably small and compressible; the arterial hypotension is not only pronounced, but reaches the lowest possible level. The phenomenon of the white line is present.

Examination of the viscera shows a normal heart and liver, but a large and tender spleen, which reaches two or three fingers' breadths below the false ribs. The reflexes are feeble but present. A fresh attack of fever may occur at this moment, exceeding 102·2° F., and in that case the symptoms get rapidly worse, the asthenia is absolute, the slightest movement becomes impossible, the temperature falls to 96·8° or even 95° F., the pulse becomes barely perceptible, and death takes place in a state of progressive algid collapse.

The total duration of these symptoms varies: the course may be very rapid, resembling an attack of cholera, so that cases of this kind have been classified under the name of *choleriform* attacks. The progress of this syndrome of suprarenal insufficiency may be more gradual, and only be fatal in about ten days' time. We have, in fact, seen transient improvement apparently due to treatment by quinine and adrenalin. The influence of adrenalin on the vomiting and diarrhœa appeared to us in some cases to be very marked; the suprarenal symptoms, however, reappeared, and the course of the disease was merely prolonged.

The syndrome of uncomplicated suprarenal insufficiency may pursue a less eventful course, and the attack may not be sufficiently severe to endanger life.

Cases of this kind may be classified in two distinct categories. In the first the syndrome of suprarenal insufficiency remains exclusively glandular, while in the second it is complicated by the pigmentation characteristic of Addison's disease.

The first group consists of recently infected patients, whose symptoms during the first invasion did not show any features of abnormal gravity. After presenting these symptoms they remain anæmic and show slight digestive disturbances, such as nausea, occasional vomiting, and anorexia, but their chief symptom is profound asthenia. They are confined to bed in a condition of prolonged immobility, and are incapable of the slightest muscular effort. Their pulse is easily compressible; with Pachon's oscillometer we found a minimum tension of 2° and a maximum of 9°. On questioning them it is found that they frequently suffer from pains in the lumbar regions. Their general condition did not appear grave; when treated methodically their symptoms appeared to improve, and the patients could be evacuated.

This syndrome of gradual suprarenal insufficiency may be completed by the appearance of pigmentation. The pigment spots are situated in the usual situation, viz., the temples, scrotum, and buccal mucous membrane. The syndrome of Addison's disease is then complete.

INTESTINAL AND PERITONEAL SYNDROMES

Diarrhœic and dysenteriform symptoms.—Intestinal disturbances are fairly frequent in malaria.

They consist of diarrhœa and dysentery. The character of the diarrhœa varies in gravity.[1]

As a rule there is merely an attack of bilious diarrhœa associated with an isolated paroxysm or a short series of quotidian attacks. The intestinal catarrh begins and ends with the fever. The patient has about ten stools in the twenty-four hours. The evacuations are abundant, liquid, bilious, mucous, and bloody. Each stool is accompanied by more or less diffuse abdominal pain, but often most pronounced along the transverse and descending colon.

The diarrhœic syndrome presents several relapses. A malarial patient who has previously had symptoms of entero-colitis during a febrile attack, is subject to fresh outbreaks on each subsequent febrile attack. It may often happen that the only manifestation of some malarial attacks is a diarrhœa, which serves as the equivalent of a malarial attack, febrile or otherwise. These outbreaks of malarial entero-colitis are improved or cured by quinine. But the intestinal disturbances in malaria may assume a more severe form, the diarrhœa being complicated by a dysenteriform syndrome, especially in patients suffering from more or less severe continued fever. The diarrhœic syndrome which at first is most in evidence is shown by very frequent bilious discharges and more or less abundant and repeated intestinal hæmorrhages, but tenesmus and rectal gripping are soon added to the phenomena of entero-colitis, the stools become more and more numerous, and take on the " frog-spawn " appearance of dysentery. The dysenteriform syndrome has now taken the place of the initial bilious diarrhœa. The patient's general condition changes, his face becomes pinched, his voice becomes weak, and he dies in a sort of typhoid state.

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[1] P. Abrami and C. Foix, *L'entérité du paludéen. Réunion des Soc. Méd de l'A. O.*, Nov. 7, 1916.

This dysenteriform syndrome sometimes occurs so early that the patient appears to be suffering from actual dysentery from the very first. The intestinal manifestations of malaria should always attract the doctor's attention, as their tendency to recur and to become chronic predisposes to a serious complication, viz., acute primary cachexia, of which we shall speak ater.

The diagnosis of the nature of these dysenteriform states is often difficult owing to the frequent co-existence of amœbic or bacillary dysentery during the season of a malarial epidemic. Apart from laboratory information, the character of the fever accompanying these symptoms will enable the course to be established in the great majority of cases.

PERITONEAL SYNDROME

The patients are sometimes brought to hospital with the diagnosis of appendicitis, as in the course of a febrile attack they are seized with vomiting and diffuse and violent lumbo-abdominal pain. The tenderness of the abdomen is so exquisite as to suggest a peritoneal reaction, especially as the pulse is often very compressible, but the presence of diarrhœa, the absence of precise localization of the pain, and the course of the symptoms which rapidly subside, negative the idea of appendicitis, which at first seems absolutely certain.

SYNDROME OF ACUTE CACHEXIA

During the period of relapses in primary paludism we have sometimes observed a syndrome of considerable gravity, viz., a sort of cachexia of rapid course, ending fatally within a few weeks.[1]

This syndrome develops in patients who have generally had only very slight symptoms during the first invasion. The symptoms merely consist of a sense of fatigue or such mild digestive disturbances and transient febrile attacks that the patient does not want to be admitted to hospital, and owing to the mild character of the symptoms the period of invasion escapes notice, and the subject does not undergo any special treatment.

During the following weeks the patient appears to become decidedly anæmic. The anæmia may occur without fever or on the occasion of a febrile attack, which seems to be the first manifestation of the malarial infection, whereas it is already a phenomenon of the period of relapses. The syndrome of anæmia pursues a progressive course, and is almost always accompanied by fever, which assumes one of the types which we have previously described, viz., the continued form, the quotidian intermittent, or the tertian variety. All these types of fever may be met with in the same subject succeeding one another without an interval of apyrexia.

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[1] G. Paisseau and H. Lemaire, *La cachexie aiguë du paludisme primaire. Bull. Soc. Méd. Hôp. de Paris,* Dec. 8, 1916.

Anæmia is not the only symptom which plays a part in this cachectic syndrome. Profound asthenia and digestive disturbances, such as vomiting and diarrhœa, rapidly supervene. At first these symptoms may be only intermittent, not developing until the outbreak of fever, and ceasing in the phase of apyrexia. During the patient's attacks of fever the vomiting and diarrhœa assume an almost uncontrollable character, the asthenia is profound, the lumbar pain is very severe, and the arterial tension is particularly low. It may often happen that these symptoms, especially the digestive disturbances, last longer than the fever, and outlive the attack which seems to have caused them. A sudden aggravation soon becomes obvious ; on the occasion of a particularly violent febrile attack the vomiting becomes more intense, the stools more frequent, and the asthenia more profound than they have ever been before. The anæmia also increases, and an icterus often appears, which, as a rule, is transient and mild and not accompanied by normal bile-pigment in the urine. Breaking up of the organism now speedily takes place, and emaciation proceeds very rapidly. The appearance of patients in a state of cachexia is particularly striking, the subject is profoundly anæmic and has an earthy, dirty yellow complexion, his mucous membranes have lost their colour, and the conjunctivæ are often subicteric. Emaciation is extreme, especially in the face, where the skin appears stuck to the bone, and the combination of all these changes gives the face a remarkable appearance of precocious senility. Asthenia is an important symptom; the patient is confined to bed, as every movement is a source of fatigue, the arterial hypotension is pronounced, the minimum tension falling to a very low level. Bed-sores develop. Digestive disturbances still dominate the scene: vomiting occurs whenever the patient attempts to take food, the diarrhœa is often profuse, and both the vomiting and diarrhœa occasionally assume a hæmorrhagic character.

Further examination of the patient shows slight enlargement of the spleen, which reaches or just passes below the level of the false ribs; the liver is also somewhat enlarged and tender on pressure, but the other viscera show nothing abnormal.

This syndrome of acute cachexia which we have only observed in malaria due to the *Plasmodium falciparum*, has almost always a fatal issue. But we have seen a case which threatened to be fatal arrested by intensive treatment with quinine associated with adrenalin. In our opinion this successful result can only be obtained when the digestive disturbances and emaciation are not too pronounced.

PULMONARY SYNDROMES

During the period of relapses and second attacks the malarial patient may present pulmonary manifestations, the clinical features of which are characteristic enough to justify their being attributed to malaria.

Four varieties of these syndromes may be distinguished.

The first, which is by far the most frequent, is a *mild form*; it is characterized either by signs of disturbance of function occurring in the course of an attack and consisting in a spasmodic and paroxysmal cough with some respiratory distress, or by signs of slight bronchitis; the former disappear with the attack, and the latter persist.

An equally frequent form is *bronchitis with pleuro-pulmonary congestion.* The patient is re-admitted to hospital for pain in the chest, cough, dyspnœa, and fever. On examination all the signs of pleuro-pulmonary congestion are found accompanied by bronchitic râles. For two or three days one does not think of malaria, as there is nothing to indicate it. But one soon becomes struck by the changing character of the stethoscopic signs, which increase, subside, or shift their position in less than twenty-four hours; the patient's symptoms and general condition present the same remissions and exacerbations. These manifestations of pleuro-pulmonary congestion are accompanied by one of the types of fever usually observed at this period of the disease. They are mild in character, and almost always end in complete recovery, often in less than a week. In some cases, however, the stethoscopic signs persist for some days after defervescence, signs of dry pleurisy or even of a slight pleural effusion being found.

The two other forms which we have observed are much rarer.

One of them suggests a *pneumonia* of the apex.

The typical signs are present, such as dulness, bronchial breathing and crepitant râles, but the sputum generally remains viscid and only exceptionally assumes the characters of that of a frank pneumonia. This form of pneumonia often relapses *in situ* or in another part of the lung. Its course runs parallel with that of the fever, and is definitely influenced by quinine.

Lastly, we may find in malaria the typical picture of *pulmonary apoplexy* which often has a rapidly fatal termination; but this complication is, fortunately, very exceptional.

Cardio-Vascular Syndromes

The circulatory system does not always escape in the course of primary paludism. We have chiefly observed disturbance of the peripheral circulation and in the extremities of the limbs. These circulatory disorders present all degrees of severity, ranging from Raynaud's disease to *symmetrical* gangrene of a considerable segment of a limb. Raynaud's disease in its attenuated form may take on the cyclical course of a malarial paroxysm with exacerbations and remissions parallel with those of the fever. In the severest cases it may be permanent and be associated with small areas of sloughing. Patients suffering from this complication, who have contracted a severe infection, find that their lesions are improved and cured by quinine.

Symmetrical gangrene of the limbs which usually involves the feet and the lower third of the legs, has a more rapid and acute course. We have seen it occur in febrile attacks of malaria, and frequently in the course of pernicious attacks.[1] The patient generally dies of malaria, but we have seen a case which recovered through the combined action of quinine and adrenalin in intravenous injections. For the sake of completeness we may mention that some cases of erythromelalgia have been attributed to malaria. The peripheral circulation is not the only one affected. The visceral arteries present lesions of endarteritis like those of the peripheral arteries, which accounts for the unexpected occurrence of visceral syndromes in acute paludism. Among the latter, especially affecting the circulatory system, we should like to draw attention to the occasionally fatal attacks of angina pectoris with changes in the coronary arteries.

URINARY SYNDROMES

Urinary syndromes are exceptional in primary paludism. The only examples of this kind which we have seen have been a few cases of albuminuria occurring at the time of the febrile paroxysms. The albuminuria was always slight and transient. As a rule the patient was suffering from decided anæmia, and had been admitted to hospital for this complication of malaria. In the patient's past history we have more than once met with an illness like severe scarlet fever which might account for a previous renal affection.

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[1] Alamartine, *Soc. des Sciences Méd. A. O.*, 1916. Paisseau and Lemaire, *Deux cas de gangrène palustre. Bull. Soc. Méd. Hôp.*, Feb. 9, 1917. Laurent Moreau, *Presse médicale*, March 22, 1917.

In three cases, however, we observed a real acute nephritis in every way resembling that of secondary syphilis including massive albuminuria to the amount of 15-30 grammes in the twenty-four hours, and a considerable degree of œdema. In two cases quinine caused the phenomena to subside rapidly. In the third case, on the contrary, it aggravated them.

Early bilious hæmoglobinuric fever.—At the height of the malarial epidemic in August and September we saw some cases of hæmoglobinuric fever in patients who were in the period of relapses of primary paludism, but these cases were exceptional. Most of the cases of bilious hæmoglobinuric fever occurred in the cold season at a later stage of primary paludism, or more frequently, in the course of secondary paludism. We will, therefore, reserve the description of this complication for the last period of the disease, where will also be found an account of the clinical features of bilious hæmoglobinuric fever of the period of relapses, the prognosis of which is always very gloomy.

NERVOUS MANIFESTATIONS

The changes in the nervous system have been specially studied in the hospitals at Salonica by our friend and colleague Dr Monier-Vinard, to whom we are indebted for the following information.

Nervous symptoms, apart from those corresponding to the meningeal reaction observed in the forms which are severe from the onset,[1] as a rule do not occur until several months after infection, and often only in the course of secondary paludism; and it is, therefore, in autumn and winter that they are most frequently observed. They may be divided into neuralgia, neuro-muscular disorders, and polyneuritis. Occasionally focal lesions of the nerve centres may be observed.

Neuralgia.—This most frequently affects the ophthalmic branch of the trigeminal nerve, and is often accompanied by trophic lesions of the eye and its appendages, as we shall see later, as well as by palpebral and labial herpes zoster. Sciatica is also a favourite localization.

All the varieties of malarial neuralgia have features in common; they are generally unilateral, present periodic paroxysms, especially in the night or morning, and are unaffected by most analgesic remedies, while they are, on the contrary, remarkably influenced by quinine.

Neuro-muscular disturbances.—These are chiefly seen in patients who have been subject to fatigue and belong to the group of cases for which Babinski has suggested the name of *physiopathic disturbances*. The symptoms are chiefly *motor*, sometimes both sensory and motor, being characterized by muscular cramps, usually situated in the calf but occasionally affecting a large number of muscles. The cramps often co-exist with febrile attacks.

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[1] Monier-Vinard, Paisseau, and Lemaire, *Cytologie du liquide céphalo-Rachidien au cours de l'accès palustre. Bull. Soc. Méd. Hôp.*, Oct. 20, 1916.

Muscular hypertonus may also be observed, being revealed objectively and subjectively by muscular rigidity frequently existing with muscular asthenia.

Exaggeration of the tendon reflexes is the rule, idio-muscular excitability on percussion is increased in the affected muscles, and electrical examination shows, according to the case, the myasthenic reaction, the myotonic reaction, and more rarely the galvanotonic reaction.

The motor phenomena are sometimes associated with anæsthesia to pricking and even to burning, with a segmental or radicular topography. Cyanosis with slight swelling of the extremities is also very frequently met with, and the patients then complain of a sensation of cold and numbness. Pollakiuria is often present, being due to changes in the excitability of the cord.

The natural course of these symptoms is to end in recovery, though this may require weeks, and often even months.

Polyneuritis.—This seems to be rarer than some authors have stated. Other toxic and infective processes which may be associated with the malarial infection must be taken into account. During the cachectic stage of the disease, however, diffuse polyneuritis may be observed, manifested in the limbs by diminution of the reflexes, wandering pains and even muscular atrophy.

Focal lesions.—These are due to the same process as the meningeal hæmorrhages and are almost always the result of a congestive attack. They are relatively rare. They may present the characters of a simple hemiparesis or a paralysis of the Weber or Millard-Gubler type. Right hemiplegia with motor aphasia has sometimes been observed.

Mental disorders.—These have been specially studied in the army of the East by our friend Dr Vinchon, who has supplied us with the following information.

Malaria, like all other infections, may be associated with mental disorders, the origin of which may be explained by the patient's antecedents, whether hereditary (degeneration) or acquired (alcoholism). These disorders, which occur in all stages of the disease, appear in several forms, such as delirious or convulsive attacks and asthenia. Moreover, the course of pre-existing psychoses is accelerated or aggravated.

The attacks of delirium are of varying duration and consist of two types: 1. *Mental confusion* with oneiric delirium. 2. *Melancholia* with anxiety without confusion.

The first form is the more serious of the two; physical signs, such as a tendency to cardiac collapse and dyspnœa, are a bad prognostic. In the second form, which is milder, the delirium may or may not disappear with the fall of the temperature; if it persists, as well as the physical disturbances, a relapse is to be feared, in which death often occurs with hyperpyrexia or with a subnormal temperature, after a fresh attack.

Convulsions, which are chiefly due to congenital predisposition are attacks resembling those of hysteria, and sometimes begin with severe pain in the splenic region. Malarial asthenia, whether it occurs early or late, is aggravated and prolonged by anæmia, but in some cases it may persist after the latter has disappeared. Malaria causes a return of attacks of periodic psychosis, a more rapid evolution of dementia, and an aggravation of hypochondriacal or persecutional delirium, based on hallucinations or delirious interpretations. The treatment is that of malaria associated with that suitable for mental disorders. Heliotherapy, as well as hydrotherapy, yields excellent results. Lastly, in the course of attacks of delirium or asthenia, malaria gives rise to medico-legal complications, especially fugues and attempted suicide.

OCULAR COMPLICATIONS.

These have been studied in a very large number of cases by our colleague and friend, Dr Chavernac, who is in charge of the ophthalmological department, and we are indebted to him for the following information. The complications may affect the nerves of the eye and its vascular system.

Symptoms of affection of the sensory nerves.—*Keratitis* is frequently observed, being closely associated with neuralgia of the trigeminal, and generally occurs from two to three days after the paroxysm which was the cause of it. It is usually accompanied by palpebral herpes and is almost always complicated by *iritis* with slight hypotonus of the eyeball.

It is superficial and slight in the case of infection by the plasmodium vivax, but obstinate and difficult to cure in the case of plasmodium falciparum infection. It may assume any of the following types: phlyctenular, vesicular, dendritic, annular, disciform, nodular, striated or ulcerative marantic.

To effect a cure it is necessary to adopt an intensive quinine treatment as well as local treatment with atropine. *Secretory disorders* may be observed in the form of lacrymation lasting several hours during the neuralgic paroxysm.

Symptoms of affection of the motor nerve.—These consist either in affection of the extrinsic muscles, such as paresis or permanent paralysis, involving especially the superior rectus, the external rectus, or the muscles of convergence, or in affection of the intrinsic muscles, causing paresis or cramps of accommodation.

Symptoms of affection of the optic nerve.—These consist of subjective phenomena, such as transient or permanent amblyopia, coloured vision (erythropsia, cyanopsia, xanthopsia), hemeralopia and hemianopsia. Hemianopsia was found to be excessively frequent, several hundreds of cases having been observed, almost exclusively in the hot season.

Quinine amaurosis, on the contrary, was exceptional, in spite of the considerable number of cases under treatment. Only one case was seen by Dr Chavernac, so that the apprehension of this complication should never be a contra-indication to the use of large doses of quinine.

Changes in the vascular system.—*Conjunctival hæmorrhages* are frequent, but have no effect on vision.

Iritis is a frequent complication of keratitis, but rarely exists as an isolated phenomenon. It is influenced by the febrile attacks, which may provoke, aggravate, or prolong it, but it subsides without leaving any trace.

Uveitis of protracted course was observed in two cases.

Chorio-retinitis is very frequent in individuals who have been infected several months previously, and appears in the form of peri-papillary deposits of pigment, the abundance of which may cause a diminution of vision. Quinine has no action upon them.

Congestion of the retina is a common occurrence in the course of an attack, the veins are swollen and the macula is dark red.

Exudations appear in the form of slight greyish films masking in places the outline of the vessels; they may even run together and form an agglomeration with circular outline.

Retinal hæmorrhages are macular or peri-papillary, and pre-retinal, intra-retinal, or retro-retinal. They usually become absorbed fairly quickly, but they may give rise to atrophy of the retina. They are easily seen with the ophthalmoscope, and are always situated in the area supplied by the short posterior ciliary arteries.

Laryngeal and aural complications.—The laryngeal complications of malaria which have been studied by our friend Dr de la Mothe are almost exclusively of a motor character. We have, in fact, never come across a case of laryngeal inflammation which could be undoubtedly attributed to malaria.

Aphonia may develop more or less suddenly, usually after severe attacks and almost always in association with marked asthenia. The voice is faint, whispering and toneless, being interrupted owing to the waste of the air column, the glottis closing incompletely.

This aphonia may be due to two causes. 1. More or less pronounced paresis of the constrictors of the glottis and tensors of the vocal cords.

2. A true recurrent paralysis of one vocal cord, which is less frequently met with and may or may not end in recovery. The prognosis is favourable. As regards treatment, one should wait until the state of asthenia has disappeared. A few courses of faradization and re-education will then be enough to restore the patient's voice.

Two other exceptional conditions have been observed :

1. A case of paralysis of the dilators of the larynx, the right vocal cord being immobilized in the median position. This phenomenon being unilateral was not accompanied by any disturbance of function. It is reasonable to suppose that in some cases this paralysis may be double, the glottis being entirely closed, in which case intense respiratory distress will develop and necessitate tracheotomy.

2. Several cases of motor inco-ordination,

difficult to interpret, in which the laryngeal disorders are associated with disturbance of speech resulting from the affection of other centres.

Auditory disturbances.—In our opinion there is not such a thing as quinine deafness. All the patients admitted to hospital with this diagnosis whom we have seen up till now were suffering from old lesions of the middle ear. Quinine causes a temporary congestion and gives rise to tinnitus, but these auditory disturbances are transient and disappear rapidly without leaving any trace.

We have had no opportunity of seeing a case of deafness from affection of the labyrinth or the cochlear nerve due to malarial infection. On the other hand, we have observed two cases of disturbance of equilibrium with loss of excitability of the vestibular nerve. Both cases improved.

3. PERNICIOUS ATTACKS

Throughout the period of primary paludism, often even within the first weeks following the invasion, the malarial patient may present symptoms of such special gravity and with such a violent and dramatic course that they have been entitled *pernicious attacks.*

This *pernicious character*, to which some writers have tried to attach a mysterious significance, is simply due to the association of two factors: invasion by a large number of parasites and diminution of the resistance of the organism. In all cases under our observation examination of the blood during life and before quinine treatment, frequently showed an enormous proportion of the red corpuscles affected by the parasite ; on autopsy the visceral capillaries were crowded with hæmatozoa always belonging to the variety of *Plasmodium falciparum.* Furthermore, persons suffering from pernicious attacks are generally men who have been subjected to overwork and fatigue.

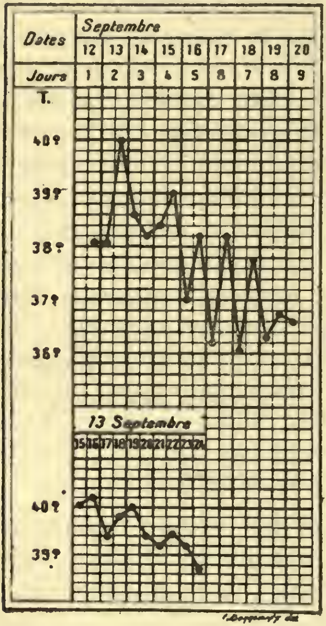

Fig. 12.—Pernicious attack, of the apoplectic type.

This intense parasitic invasion, associated with these causes of breaking down of the organic resistance, offers an explanation of the profound lesions always observed in some viscera such as the nerve centres and the suprarenal capsules.

The pernicious attack generally occurs in an individual who appears to be in perfect health and is suddenly taken ill while engaged in his ordinary duties. But it may also develop in a patient already under treatment for some malarial manifestation. A rapid and unexpected aggravation ensues, which may cause death in less than forty-eight hours.

It is usual to describe a large number of types of pernicious attacks, *e.g.*, the cerebral, algid, delirious, bilious, diaphoretic, choleriform, gastralgic, cardialgic, dyspnœic, etc.

We will describe only two sorts of pernicious attacks, viz., the *cerebral attack* and the *algid attack*, for the cases which we have observed, and which might be regarded as other forms of pernicious attacks, did not seem to us to present a sufficiently violent and rapid course to justify their classification among these forms of malaria.

Cerebral forms.—The cerebral attack presents two clinical types: *the apoplectic attack* and *the convulsive attack.*

Apoplectic attack, insolation type.—The patient is suddenly seized in the middle of his work with symptoms resembling those of heat stroke. He has merely been complaining of fatigue, headache, and insomnia for a few days, when all of a sudden he becomes giddy and falls down in the road in a state of apoplexy. His face is bloated and his respiration sighing. He presents conjugate deviation of the eyes and complete muscular relaxation. The last symptom, however, is often succeeded by slight hypertonus, especially in the upper limb, as indicated by flexion contracture of the forearm: the deviation of the head and eyes is not always conjugate, but is often opposed. These two symptoms indicate a cortical localization with a meningeal reaction, which is confirmed by the existence of a cerebro-spinal lymphocytosis.

The patient's temperature rises at once 103·2° or 104°, or even 105·8° F. Death may occur in a few hours. In other cases some improvement may take place in twelve to eighteen hours' time. The patient gradually wakes up out of his torpor, asks some questions and calls for a drink. If examination of the blood has been made and any kind of injection of quinine has been given, especially an intravenous one, improvement takes place very rapidly, the temperature falls progressively in two or three days, or on the other hand the patient remains febrile and presents a sub-continuous fever, which is usually very little affected by quinine. This apoplectic attack is sometimes accompanied by signs of focal lesions, *e.g.*, hemiplegia or aphasia.

Hemiplegic variety.—In some cases a unilateral predominance of the symptoms of paresis may be found at the time of the loss of consciousness, constituting an actual hemiplegia or hemiparesis. The course is the same as in the previous case. The paretic phenomena disappear entirely under the influence of quinine, and the patient recovers consciousness simultaneously.

Aphasic variety.—Before the comatose period or when it is passing away, some patients may show, either with or without a right-sided paresis, symptoms of motor aphasia, which may last some hours, but also yield to treatment.

Convulsive meningeal form.—The pernicious attack starts with convulsive phenomena of the epileptiform type, which may simulate a true attack of epilepsy; there is also contracture of the limbs, nuchal rigidity, and sometimes conjugate or dissociated deviation of the head and eyes, accompanied by persistent coma with a rise of temperature to 104° or 105·8° F. Examination of the blood and discovery of the causal agent lead to the adoption of quinine treatment. We may add that in these cases the cerebro-spinal fluid shows considerable lymphocytosis, definite albumin, and slight hypertension.

In some cases transient coma is met with, accompanied by icterus, vomiting, and bilious diarrhœa. These phenomena correspond to the *bilious attack* described in textbooks.

Algid form.[1] — In this well-known form of pernicious attack the patient's appearance is characteristic; the initial symptoms are often the same as in an ordinary attack, but the fever is particularly high. It is accompanied by nervous disorders, which are sometimes intense, delirium, and almost uncontrollable vomiting.

But the picture suddenly changes completely, the temperature drops, falling to 96·8° and lower, and the various symptoms of algid collapse set in.

The patient then presents a characteristic appearance. He remains quite still, in a condition of profound asthenia, the face is drawn, the eyes sunken, fixed and expressionless; the nose pinched and the voice hoarse. The face is often discoloured by violet patches, the extremities of the hands and feet are cyanosed and cold as ice, the skin covered with clammy sweat, and the respiration is shallow. The pulse is only slightly accelerated, and is small and compressible, and the arterial pressure is very low; we have noted the phenomenon of the white line. The heart sounds keep their normal rhythm, but are simply weakened.

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[1] Paisseau and Lemaire, *Accès pernicieux palustres et surrénalite aiguëe. Bull. Acad. Méd.*, Oct. 17, 1916, and *Bull. Soc. Méd. Hôp.*, Oct. 13, 1916.

This syndrome of algidity and hypotension is very often associated with a series of secondary symptoms chiefly affecting the alimentary canal. There is repeated vomiting, accompanied by profuse diarrhœa and lumbar, abdominal and epigastric pain, and the patient often complains of painful cramps. The picture of a choleriform attack is thus complete. Death may occur suddenly, consciousness being retained till the end. When the attack ends in recovery, which is exceptional, the arterial tension rises as well as the temperature, the extremities become warm again, and abundant perspiration develops, marking the end of the attack. The algid attack is of the utmost gravity, but there is, nevertheless, some hope of saving the patient by the combined action of quinine and adrenalin in intravenous injections.

4. DEFACED PALUDISM AND MASKED PALUDISM

Defaced paludism.—Defaced paludism may be regarded as an attenuated form of malarial infection. It is found in persons who have been only very slightly exposed to infection, or in those living in easy circumstances and possessing a sort of natural immunity. It is a kind of almost apyretic paludism, in which the visceral localizations are few and slight. The initial manifestations consist of an ill-marked febrile malaise. They may be so trivial that they pass unnoticed by patients who do not pay much attention to their ailments.

Subsequently, instead of the febrile attacks of the period of relapses and second attacks, the patients have incomplete attacks only. Fever, though often denied, is not completely absent, but is slight and curtailed ; it has, as a rule, completely disappeared when the other symptoms attract the patient's attention. These symptoms are mostly of a subjective character, such as neuralgia, headache, lassitude, and asthenia, which are succeeded by a sense of well-being. Close examination suggests a certain degree of anæmia, which is confirmed by hæmatological examination, and can often be found in this way even in persons of florid appearance. This anæmia has the hæmatological appearances of the malarial anæmia which we described above. It consequently possesses a real semeiological value. Its presence, if it does not actually warrant a certain diagnosis of malaria, at all events suggests it, even in the absence of the hæmatozoon, which is often not present in this form.

Masked paludism.—In masked paludism visceral manifestations take the place of febrile phenomena, which are almost entirely absent.

It is a form of paludism which runs its course without fever. During the period of invasion the symptoms are reduced to a minimum ; the patient only complains of headache, vague digestive disturbances, with nausea, anorexia, fatigue, slight asthenia, and some lumbar pain, all of which he attributes to the heat and overwork.

He has already forgotten these symptoms when several weeks and even several months later he presents various non-febrile disorders, which do not in any way suggest malarial manifestations, such as disturbances of the nervous system, organs of special sense and viscera.

Anæmia is certainly the most usual manifestation of masked paludism. As its malarial origin is easily overlooked in the absence of characteristic febrile phenomena, it gradually assumes its most pronounced features, giving rise to the severest clinical and hæmatological forms. This anæmia of masked paludism assumes the type of hæmorrhagic anæmia or pernicious anæmia which we have described. It is often the prodromal stage of acute cachexia. Masked paludism may also consist of nervous phenomena only, especially of a peripheral character, or neuralgias of the type which we have described above, and manifestations of the organs of special sense, particularly the eye.

CHAPTER V

SECONDARY PALUDISM

SECONDARY paludism is characterized by the appearance of *disciplined febrile attacks*, which are also called *frank attacks* (ague fits).

We adopt the term "disciplined," because it exactly expresses the regularity of the temperature curve of the attack, which is closely connected with the biological evolution of the parasite within the organism. This evolution is one of the best established conceptions of the parasitological study of the hæmatozoon. This is the schizogonic or parthenogenetic evolution, the cycle of which is completed in forty-eight hours. It is the asexual cycle which we described above in the chapter on parasitology.

The regular succession of these evolutional cycles gives rise to typical tertian intermittent fever; but under the action of various causes (increase in resistance of the organism, or quinine treatment) it may be interrupted.

It can readily be understood that secondary paludism can only assume this disciplined character if the patient is not exposed to fresh inoculations.

It is therefore the kind of paludism met with in persons who have returned to a non-malarial district, or one which in the case of infected countries only appears in the cold season after disappearance of the mosquitoes which propagate the virus.

It should not be forgotten, however, that some persons make their first acquaintance with malaria in its secondary period. Such is the typical history of the colonial who has his first attack on returning home, as frequently occurred among the soldiers in the army of the East. As a rule, the patients are those in whom the symptoms of the first invasion were very slight and passed unnoticed; sometimes, however, the patient on being questioned has no recollection of any malaise, and it is possible that the primary period really has no symptoms.

The ague fit being the essential element in the febrile curve of secondary paludism, we shall describe it first of all. We shall then show how these attacks may recur, and take place at longer or shorter intervals, thus giving rise to a variety of temperature curves.

Previous visceral lesions may leave sequelæ, which will appear again in this secondary period of paludism, and will be revealed by symptoms which are usually attenuated.

The ague fit.—A man who appeared to be in good health or only slightly anæmic, is suddenly seized, usually late in the forenoon, with violent shivering and malaise so that he is compelled to lie down. His teeth chatter, and he shakes from head to foot. His face is pale, his look anxious, and his eyes bright. The pulse is quick, and the extremities cold. The temperature meanwhile has risen to 100·8°. But in about half an hour's time the patient, who had rolled himself up in his blankets to get warm, begins to feel a sensation of intolerable heat. At the same time an intense headache sets in, often accompanied by pain in the back; the skin is dry and burning. The cheeks are flushed, the patient complains of dryness of the throat and intense thirst which even iced water cannot quench. The temperature rises rapidly to 104° or above.

There is an acute feeling of discomfort, which is often accompanied by nausea and even vomiting.

This condition persists for two or three hours, and then an abundant and profuse perspiration breaks out.

The patient then experiences a sensation of well-being. He covers himself again to avoid the chilling caused by the sweating, which stops in an hour's time. The fever has then fallen below 100·8°, but the normal temperature is only reached about 10 p.m., about twelve hours after the onset of the shivering.

The patient now falls asleep, passes a good night, and the next day thinks that he is cured, although he feels a little languid. The temperature is normal, and he resumes his occupation until the onset of the next fit, which will be identical with the preceding.

A close study of the temperature taken every half hour, shows, as we have said, that at the beginning of the fit it is already 100·8° F. Then it rises suddenly to reach its acme, which is about

104° less than an hour after the onset of the fit. It remains at this high level for two and a half to three hours, and then after commencement of the sweating stage it falls to 100·8°, and slowly returns to normal, eleven to twelve hours after the onset of the fit. The ague fit, as all the text-books state, runs its complete course between two *meridians*, commencing about midday and ending before midnight.

1. PRINCIPAL TYPES OF TEMPERATURE CURVES

The ague fits are generally grouped so as to constitute tertian or quartan fever,[1] each fit being separated from the following by an apyrexial interval of one day in the case of tertian fever and of two days in that of quartan fever.

But the fit may remain isolated or only take place at longer intervals, of about a week's duration. On the other hand, it may form an uninterrupted series of quotidian fits, thus constituting a quotidian intermittent. Lastly, the temperature curve in secondary paludism sometimes shows a very irregular character.

(1) **Tertian intermittent fever.**—This is the typical curve of secondary paludism: the fit takes place every two days with an interval of thirty-six hours of normal temperature. It should be noted, however, that this interval of forty-eight hours between the onset of each fit may be pro-

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[1] We shall not give a description of quartan fever, which has not been found hitherto in Macedonia, and which we have only seen in persons coming from Algeria.

longed or shortened (forty-seven to forty-nine hours) according to the individual. This peculiarity, to which Italian writers have drawn attention, is of importance in determining the exact moment for administering the dose of quinine for cutting short the fit.

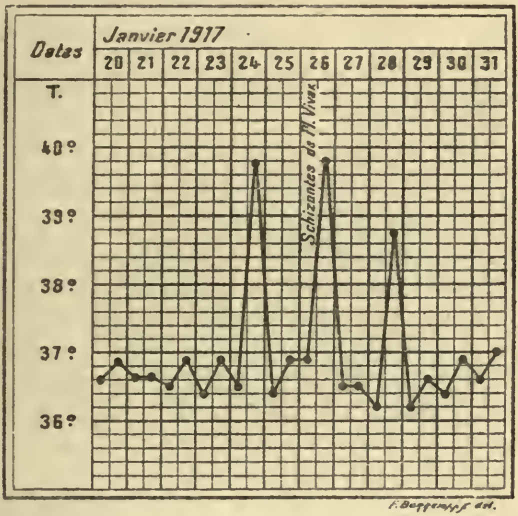

Fig. 13.—Secondary paludism. Tertian intermittent fits.

The temperature curve of tertian intermittent fever may vary considerably in length according to the progressive immunization of the organism and its resistance. The diminution in vitality of the parasite is also expressed by a diminution in the intensity of the successive fits. Lastly, quinine treatment is almost always successful in these cases.

(2) **Ague fits of septan type.**—For reasons hitherto unexplained, the fits instead of assuming the tertian type may only recur every six or seven days, even in the absence of any quinine treatment. In other cases they recur only every fortnight or every three weeks, giving rise to what has been called fits of the bi- and tri-septan type.

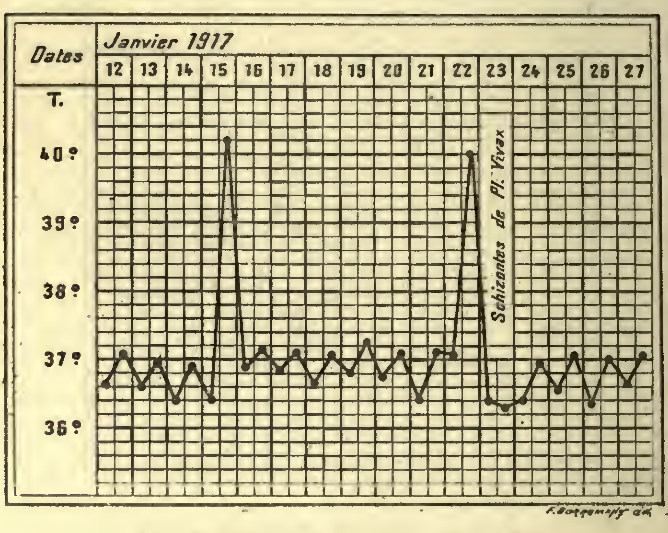

FIG. 14.—Secondary paludism. Septan fits.

(3) **Isolated fits.**—The fits may even appear to be absolutely isolated. After apyrexia for one or even two months, on the occasion of fatigue or a chill, and sometimes even without any appreciable cause there is an isolated fit which will not be repeated for a long time.

(4) **Quotidian intermittent fever.**—This is due, as Italian writers have shown, to the combination

of two tertians running their course with an interval of twenty-four hours between them. They are caused by the evolution of two generations of parasites developing at twenty-four hours' interval. There is a febrile attack every day instead of every two days, but as the first begins shortly before midday and ends before midnight, the temperature in the morning is normal, which accounts for this type of quotidian intermittent.

Irregular fever.—In some cases the temperature curve does not seem to correspond to any definite type, and its course is very irregular. But if the temperature is taken at least four times a day, it will be found that the fever really reproduces the temperature chart of a quotidian intermittent, whereas if the temperature be taken only twice a day the maximum and minimum temperatures are not indicated.

2. Clinical Syndromes

The clinical manifestations observed in the course of secondary paludism are much less frequent than in the period of relapses and second attacks of primary paludism. Their gravity is also much less. It is undoubtedly possible to meet with the same visceral syndromes as those which we described in primary paludism, but they are generally much attenuated, and in actual practice we have hardly seen more than three varieties, viz., anæmia, nervous disorders, and bilious hæmoglobinuric fever.

Anæmia.—Anæmia, which was one of the most important visceral manifestations of the period of relapses, still remains one of the principal phenomena. But it never attains the degree of severity or assumes the pernicious character which it has during the period of a malarial epidemic. It retains, however, the same clinical and hæmatological characters, although the œdema and hæmorrhages are not often seen. A slight degree of icterus is the only phenomenon which is fairly commonly met with, its outbursts succeeding those of anæmia.

Nervous Disorders are not exceptional. They are mainly due to affection of the peripheral nerves and are neuralgic in nature. Focal lesions of the central nervous system, however, have been observed at this period and are indicated by paresis and motor aphasia; affection of the meninges is revealed by lymphocytosis and even hæmorrhage. For further details we will refer the reader to our previous description.

BILIOUS HÆMOGLOBINURIC FEVER [1]

Bilious hæmoglobinuric fever is fairly characteristic of secondary paludism. Though we have observed a few cases at the height of an epidemic, the affection is most frequent when the attacks show a tendency to become disciplined and when the individual is no longer exposed to fresh inoculations.

We will choose as the type for our description the bilious hæmoglobinuric fever which we observed in winter during the month of January.

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[1] Armand-Delille, Paisseau, and Lemaire, *Caractères de la bilieuse hémoglobinurique chez les Paludéens de l'Armée de l'Orient. Bull. Soc. Méd. Hôp.*, June 15, 1917.

The patient is almost always undoubtedly malarial, and is more or less anæmic in consequence. Periodically and according to a fairly regular rhythm he presents isolated febrile attacks or a series of two or three with a tertian grouping. The attack of bilious hæmoglobinuric fever generally breaks out in place of the expected ague fit on the day foreseen by the patient and his doctor.

The individual is suddenly seized with violent shivering, severe headache, and pain in the loins. He suffers from nausea and vomiting, and has the same malaise as during each of his ague fits, but in a more intense degree. The fever also rises higher than usual and exceeds 104° F. In the two or three hours following the onset of the attack, before these various symptoms have had time to subside, the patient suddenly feels a desire to urinate, and his urine is red and blood-stained. The following specimen passed is darker and of a port-wine colour. The patient is now overcome by a general feeling of lassitude and takes to his bed.

Icterus sets in a few hours after the bloody urine has been passed. It is rarely limited to the conjunctivæ, but extends all over the skin and mucous membranes, getting darker during the first twenty-four hours.

Examination of the viscera shows only a slight enlargement of the spleen which was already present before the attack, the organ just reaching the costal margin and being tender on pressure. The liver is also slightly enlarged, just reaching below the false ribs and is also tender on pressure. The course of the affection varies, but as a rule the bilious hæmoglobinuria of the secondary period ends in recovery. The following day the patient's general condition is already improved, and he is less febrile, though he still has some anorexia, slight headache, lumbar pain, and a feeling of lassitude; on the following day the temperature returns to normal, but the attack still persists and gradually subsides in a week.

The urine on the first day is very dark and scanty, its quantity not exceeding 500-800 c.c. It is coloured red owing to a large quantity of hæmoglobin, but does not contain red cells. Its amount soon increases and returns to normal in the course of the following days.

The hæmoglobin diminishes, but the urine instead of getting clearer, becomes icteric and full of normal bile pigment. Examination of the urinary sediment after the first urine has been passed shows a few fragments of red corpuscles and when a larger amount of urine has been passed much cellular debris and even epithelial casts are found. The kidney ceases to be blocked and desquamates after having allowed the hæmoglobin to filter through.

The changes in the blood serum present a similar cycle. Examination of the blood made at the beginning of the attack shows the existence of considerable hæmoglobinæmia, the blood is laked, and the following day the serum becomes icteric and the free hæmoglobin disappears. The study of the globular resistance yields interesting results;

it is much diminished in the first few hours of the attack of bilious fever, the red cells become dissolved in normal saline solution, and then their number rises rapidly to normal (4·2 per 1000). But the patient is very anæmic. It is not uncommon to see him lose a million red cells in the course of an attack.

The affection may present two different modes of evolution. When it is to end in recovery, which occurs in most of the cases in secondary paludism, the urine becomes clear, its amount increases, the fever falls, and all the discomfort progressively subsides; the icterus disappears in a few days. The patient remains anæmic. In some cases the attack of hæmoglobinuria may recur after a period of twenty-four or forty-eight hours in which the urine remains clear. The temperature rises again and the patient again has urine of a port-wine colour, but the second attack is generally shorter and convalescence becomes rapidly established.

In fatal cases of bilious hæmoglobinuria death is due to anæmia. After the second or third day there is suppression of urine and the patient develops uræmic coma or more frequently a gastro-intestinal form of uræmia, which may last for a week. This severe course is rare during the secondary period of paludism, and is much more frequent during the height of a malarial epidemic from July to September. This form, which belongs to the period of relapses of paludism, presents a more severe course, and severer functional symptoms. Examination of the blood shows that it is as rich in parasites as during an ague fit.

CHAPTER VI

ASSOCIATION WITH OTHER INFECTIONS

VARIOUS infectious diseases may occur in the course of primary and secondary paludism, especially typhoid fever, paratyphoid fevers, bacillary and anæmic dysentery, and recurrent fever.

Typhoid fever.—The subjects in our field of observation had generally been vaccinated against typhoid and paratyphoid fevers, and on that account association of malaria with other dieases was rarely observed. In the cases in which the co-existence of these diseases was proved by bacteriological examination (positive typhoid blood culture with presence of hæmatozoa in the smears), the temperature curve and the course of the disease were dominated by the more powerful infective agent, in this case the hæmatozoon.[1]

In non-vaccinated cases, on the contrary, the clinical appearances in this association of diseases were those of enteric fever.

Dysentery.—Bacillary or amœbic dysentery occurring in a malarial subject aggravates his case, causes a return of the febrile attacks and predisposes to chronic intestinal lesions and malarial cachexia of the secondary period of paludism. We would emphasize the necessity of a simultaneous examination for both parasites, hæmatozoa and amœbæ, in the blood and the stools, in view of the possibility of a dysenteriform enteritis of purely malarial origin ; we have, indeed, seen cases of true dysentery which bacteriological and parasitological examination carried out under the most favourable conditions proved to be connected neither with amœbiasis nor bacillary dysentery, but which occurred paroxysmally in malarial patients whose blood was infected by the hæmatozoon.

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[1] Armand-Delille, Paisseau, and Lemaire, *Paludisme de* 1^re^ *invasion en Macédoine. Bull. Soc. Méd. Hôp.*, March 3, 1916.

Recurrent fever.—An association of malaria with recurrent fever may possibly take place.[1] The manifestations of secondary paludism being observed in Macedonia in the winter and spring, it is easy to understand its co-existence with this affection which is so frequent in the cold season. Paludism has no influence on its course, but we have, on the other hand, frequently seen malarial patients have tertian fits in the days following the relapse of recurrent fever.

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[1] Armand-Delille, Gassin, and Lemaire, *Caractères de la fièvre récurrente observée à l'Armée de l'Orient. Bull. Soc. Méd. Hôp.*, June 15, 1917.

CHAPTER VII

PARASITOLOGICAL DIAGNOSIS

WE shall naturally confine ourselves to a description of the essential requirements for diagnosis, and shall only mention the technique which can be carried out in the most rudimentary laboratory.

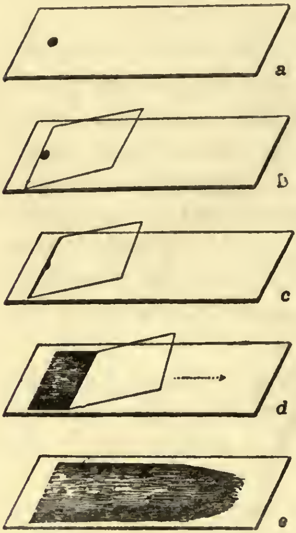

FIG. 15.—Method of making a blood film (after Langeron).

The examination for the hæmatozoa of malaria is made on *dried and stained blood films.* It is important to realize that this examination must be a very careful one; on the one hand, the proportion of positive results does not exceed 40 per cent., especially in subjects on preventive quinine treatment, while, on the other hand, with certain exceptions which we shall mention later, the number of circulating parasites is unusually small. The blood intended for examination should be taken either from the lobe of the ear or the dorsal surface of the finger near the matrix of the nail; the skin of these regions should be very carefully wiped, as the mixture of sweat with the blood gives very bad preparations. The part should be pricked with a pin which has been passed through the flame and a very minute droplet of blood should be squeezed out, collected on a very clean slide near one of its extremities, then spread out either by a sterilized slide or a visiting card, in a very fine film, and lastly dried by waving it rapidly to and fro. After having carefully wiped the region which has been pricked a second droplet of blood should be collected, spread out and dried in the same way; except when there are special indications two good slides are sufficient each time the blood is taken.[1]

As soon as the slides are dry they should be wrapped up in paper to keep them from flies, which are very fond of blood and can completely change and spoil a preparation by repeatedly sucking it. The patient's name and any clinical notes of interest should be written on the wrapper. All the methods of staining at present in use are improvements on the processes of Laveran or Romanowski.

The preparations are easily stained *by Tribondeau's method,* provided the recommendations are strictly adhered to, which the writer took care to transcribe on the notice accompanying the bottle containing the stain. It runs as follows :—

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[1] *v.* p. 95, for the technique of the so-called "thick drop process."

DIRECTIONS FOR USING TRIBONDEAU'S BI-EOSINATE.[1]

"Use carefully cleaned slides for preparing the films; spread the blood (or organic fluid) in a thin layer over the right two-thirds of one surface by 'the visiting-card process' by choice. Dry by shaking in the air. Do not use heat or any fixative. Mark off the smear on the left by a line with a pencil for writing on glass.

"The bi-eosinate is both a fixative and a stain.

"For fixing, drop 0·2 c.c. of bi-eosinate (about twelve drops) on the smear with a special pipette reserved for this stain. Place the slide flat on the table, cover it with a half of a Petri's capsule to avoid, especially in summer, too great an evaporation of the alcohol, which would cause immediate precipitation of the stain on addition of water, and then leave for two or three minutes.

"For staining, hold the slide slightly inclined, so as to collect the bi-eosinate on one of the long margins, add 0·6 c.c. of distilled water (about twelve drops) to the stain, mix the two fluids together all over the surface to be stained by a few rolling movements. Then put the slide down at once and don't touch it until the staining is complete, for moving it might hasten the formation of a precipitate which would spoil the result. Average time required for staining: blood, eight to twelve minutes; syphilitic products, twenty to twenty-five minutes.

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[1] Avoid the use of any trace of acid or base (as in neutral stains). Mount without a cover-slip. In case of a fine precipitate spoiling a permanent preparation, it can *rapidly* be removed with 80 per cent. alcohol, and the coloration restored by pouring very dilute bi-eosinate on the slide (0·1 c.c. to 2 c.c. of distilled water).

"Finally, wash under a jet of distilled water, without first employing the staining fluid, so as to avoid fixation of the surface film on the preparation. Shake the drops off, and dry rapidly with cautious use of a flame."

Borax-eosin-blue stain.—We warmly recommend the method invented by Senevet, which yields uniformly good results, and possesses the great advantage of requiring only the ordinary reagents, methylene blue and eosin.

The following details of this excellent method, will, we think, be of some assistance to laboratory workers:—

1. Prepare the two solutions A and B.

A. Methylene blue, 1 part.
Sodium borate, 3 parts.
Distilled water, 100 parts.

Leave in the incubator for a week to a fortnight, or three weeks, at the ordinary temperature.

B. Eosin in water, 1 part.
Distilled water, 100 parts.

Ready for use.

Fix the films in 90 per cent. alcohol, or better still in absolute alcohol for at least five minutes, and after complete desiccation of the alcohol, place them face downwards on some horizontal supports (Petri's capsule, test tubes, etc.).

Prepare the following solution in a very clean glass:—

Distilled water, 20 c.c.
Solution B, 1 drop.

Mix well, then add

Solution A (methylene blue), 1-2 drops.

Mix well, and pour at once on the films. About 1-2 c.c. per film are needed.

Stain for 2-3 hours, wash rapidly under the tap, dry, and examine.

N.B.—It is best always to have a fresh solution of methylene blue, so as not to run short, if the ordinary solution is exhausted or has lost its staining capacity.

Always use the same pipettes for measuring the drops of eosin and methylene blue, otherwise the proportions would be too variable.

It sometimes happens that after having yielded excellent results for some time the methylene blue solution stains the protoplasm of the hæmatozoa too faintly. Two remedies are available: 1. Use a fresher solution. 2. Substitute some drops of a fresh solution for some of the old solution.

Make sure first of all that the failure is not due to the acidity of the water employed.

Important Note.—It very frequently happens that so-called distilled water contains more or less strong traces of acid. This acidity of the water is the cause of failure, or of a change in the stain.

To avoid this accident, use water which is absolutely neutral or even by preference very slightly alkaline. Various processes are to be recommended for this :—

(*a*) Boil the distilled water in a glass flask.

(*b*) Use rain water or melted snow.

(*c*) Add drop by drop to the distilled water, increasing quantities of a 5 per cent. solution of borate of soda, or a 1 per cent. solution of carbonate of potash, until good results are obtained (an excess of alkalinity has the drawback of injuring the structure of certain elements, especially the nuclei of the leucocytes).

The best method for deciding whether distilled water is absolutely neutral is that described by Langeron, who uses as a reagent the alcoholic solution of hæmatoxylin: add two drops of a 1 per cent. alcoholic solution to 10 c.c. of the water to be tested, and add drop by drop a solution of 1 per cent. sodium carbonate until in five minutes' time the water becomes of a faint but definite violet colour.

(*d*) Try the ordinary water available and which sometimes gives excellent results. If the staining is successful, the following results should be obtained.

1. *Faint staining*, a drop of methylene blue (dark violet colour of the stain).

The blood corpuscles are stained pale pink or red. The nuclei of the leucocytes are violet. The neutrophils show very fine granulations of a violet colour. Those of the eosinophils are of the same colour as the red cells, sometimes even of a lighter pink. The protoplasm of the mononuclears is pale blue, and that of the lymphocytes dark blue. The hæmatozoa are very distinct owing to their purple nucleolus and pale blue protoplasm. The forms of division of benign tertian have a darker protoplasm and more intensely coloured nucleoli.

In the sexual forms the grains of pigment are very clearly seen, as well as the more diffuse and as a rule less highly stained nucleolus.

Schüffner's dots, which are sometimes fine and distinct in the medium-sized forms, are more distinct in the sexual forms (gametes).

2. *With deep staining.* With two drops of methylene blue (blue violet colour) the red corpuscles appear copper-coloured or lilac. At the same time all the staining already described is much more intense, especially as regards the nucleolus, the protoplasm of the hæmatozoa, and Schüffner's dots, which are found in some successful preparations, even in the corpuscles invaded by schizonts.

The last stain, although less pleasant to look at on account of the coppery appearance of the red corpuscles, is nevertheless to be recommended for examining the hæmatozoa, their discovery being greatly facilitated by the intensity with which they are stained.

Intermediate staining may be obtained by varying the proportions of the methylene blue and the eosin, *e.g.* by mixing three drops of methylene blue with two drops of eosin.

Laveran's panchrome.—Laveran's panchrome may also be recommended, as it gives excellent results, but we have not personally had occasion to use it.[1]

We may also mention that these methods admirably stain the spirilla of Obermeyer, and the diagnosis of recurrent fever can easily be made on a slide intended for examination of the hæmatozoa.

The examination of the blood films enables the three hæmatozoa of malaria to be distinguished from one another, viz.: the *Plasmodium vivax*, or agent of benign tertian; the *Plasmodium precox* or *falciparum*, the agent of so-called tropical fever or malignant tertian; and the *Plasmodium malariæ*, the agent of quartan fever. Sometimes two of these parasites will be found to be associated. We will now describe their distinctive characters.

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[1] *v.* p. 95, for the technique of this method.

DIAGNOSTIC CHARACTERS OF HÆMATOZOA

1. PLASMODIUM VIVAX

The *Plasmodium vivax* is the parasite most frequently met with during the cold season (from December to June); in summer, on the contrary, it was found in less than **20** per cent. of the cases. It is recognized by the following characters :—

(*a*) The blood corpuscle invaded is usually the seat of three important changes: it is increased in size, decolorized, and sprinkled over with small violet-red granulations known as Schüffner's dots.

(*b*) The *parasite itself* appears in four different aspects, according as it is young (schizont), adult (amœboid body), in course of schizogonic division (rosette body), or in the state of a gamete (macro- and microgametocytes). Specimens of each of these stages are frequently found in the same preparation.

(*c*) *The schizont*, a young form of the plasmodium, appears in the form of a small ring generally ovoid rather than rounded. At the narrowest pole, a small mass of violet red represents the nucleus,

EXPLANATION OF PLATE

PLASMODIUM VIVAX (Var. tertiana Laveran).

1. *Young schizont* (sporozoite just penetrating the corpuscle).
2. *Schizont.*
3. *Amœboid body* in an enlarged corpuscle presenting Schüffner's dots.
4. *Amœboid body* in course of segmentation in a much enlarged corpuscle.
5. *Rosette body.*
6. *Young macrogamete.*
7. *Adult macrogamete.*
8. *Microgametocyte.*

8 *bis. Macrogamete* undergoing retrogressive schizogony.

PLASMODIUM FALCIPARUM (Var. parva-Laveran).

9. *Sporozoite* attached to a corpuscle.
10. *Two schizonts* inside a corpuscle.
11. *Schizont* in a corpuscle presenting Maurer's dots.
12. *Three schizonts* in a corpuscle with Maurer's dots.
13. *Rosette body.*
14. *Young intracorpuscular gamete.*
15. *Adult macrogamete* (crescent type).
16. *Adult macrogamete* (microgametocyte).

16 *bis. Gamete* possibly undergoing retrogressive schizogony.

PLASMODIUM MALARIÆ (Var. quartana Laveran).

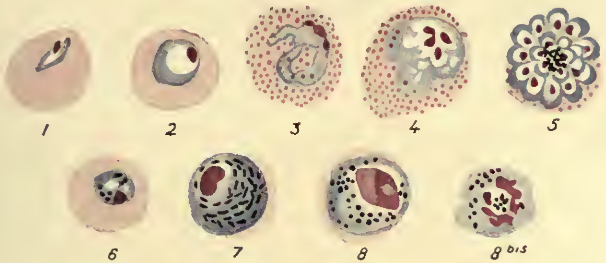
17. *Young schizont* in a non-enlarged corpuscle.
18. *More developed and pigmented schizont.*
19. *Pear-shaped schizont.*
20. *Old schizont,* much pigmented.
21. *Schizont,* undergoing segmentation.
22. *Daisy body.*
23. *Macrogamete.*
24. *Microgametocyte.*

RED CORPUSCLES (Hæmatoblasts and leucocytes).

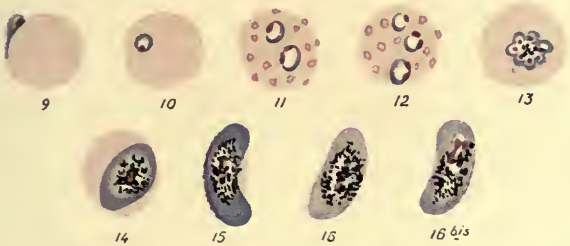
(*a*) *Red corpuscle and hæmatoblast.*
(*b*) *Hæmatoblast* in a red corpuscle simulating a schizont.
(*c*) *Red corpuscle* presenting artificial granules (precipitated colouring matter), with a hæmatoblast on its margin (cause of error).
(*d*) *Nucleated red corpuscle.*
(*e*) *Polymorphonuclear leucocytes* with neutrophil granulations.
(*f*) *Deformed mononuclear leucocytes.*
(*g*) *Melaniferous leucocytes* with some azurophil granules.

Malaria Parasites.

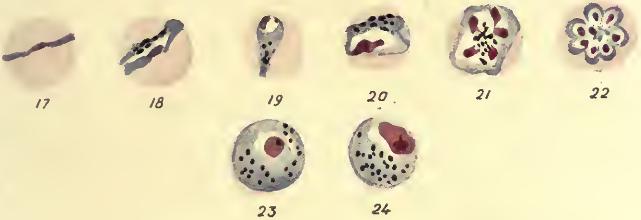
Tribondeau's Stain



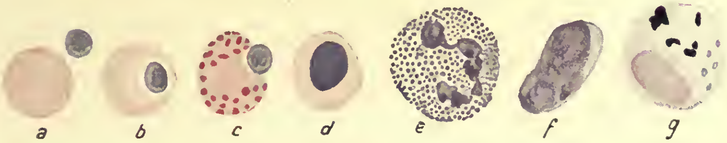
Plasmodium vivax. (var. tertiana Lav.)



Plasmodium falciparum = præcox.
(var. parva Lav.)



Plasmodium malariæ. (var. quartana Lav.)



Red corpuscles. Hæmatoblasts. Leucocytes.

P. Armand-Delille, Del.

while a rounded colourless vesicle situated between this nucleus and the protoplasmic zone coloured blue, which limits the contours of the schizont, represents the nutritive vesicle.

(*d*) *The amœboid body* is merely a schizont at a more advanced stage of development. The parasite then occupies the third, the half, or two-thirds of the blood corpuscle. It is formed of two parts, one of which encloses the nucleus surrounded by a clear pink zone, the nuclear vesicle, while the other is constituted by a mass of protoplasm, containing a large nutritive vesicle ramifying in numerous slender pseudopodia, the arrangement of which varies. In these forms (large forms) the pigment is abundant and is disseminated in the protoplasm. Schüffner's dots are numerous.

(*e*) *The rosette body*, when well formed, appears as a rounded mass, filling the whole corpuscle and roughly resembling a daisy. It is constituted by the agglomeration of 16-20 merozoites, set close together round a mass of central pigment. Each merozoite consists of a large nucleus surrounded by a thin zone of protoplasm.

Side by side with the typical rosette bodies, less advanced divisional forms are to be found, intermediate between the preceding and the amœboid bodies from which they are derived. The parasite is rounded as if it were contracted, its protoplasm stains a deeper blue, the pigment is spread out into wavy lines, the nucleus is divided into two or three or more distinct portions, and the nutrient vesicle has disappeared.

(*f*) The *gametes*, or more strictly speaking the *gametocytes* (for the transformation into sexual elements will only take place in the alimentary canal of the mosquito), are easily recognizable. Some which are in process of formation (young gametocytes) are still enclosed in the corpuscles, while the others which are mature are free in the blood.

The young gametocytes which are still enclosed in the corpuscles are ovoid or polygonal; their nucleolus is very large but of loose structure; the protoplasm is deeply coloured and does not show a nutritive vacuole, but contains numerous elongated pigment granules. The mature gametocytes are big rounded elements, twice as large as a red corpuscle. Their nucleus is of considerable size; their protoplasm contains numerous pigment granules arranged like needles. The macrogametocytes or future female elements can be differentiated by their nucleus being rounded and presenting a granular structure and the pigment being uniformly distributed over the protoplasm. The pigment often predominates round the nucleus; the protoplasm is more faintly stained.

It is important to realize that:—

1. The *Plasmodium vivax* is almost constantly found in the peripheral blood during the febrile attacks and generally in large quantities. 2. In the intervals it is still frequently present. 3. Although the parasitic forms found are, generally speaking, different according to the stage of the attack (the rosette body during the attack, and the schizont and amœboid body before it), and the gamete during prolonged periods of apyrexia,

as a rule a mixture of all the forms will be found in various proportions in the same preparation.

2. PLASMODIUM FALCIPARUM (PRECOX)

The *Plasmodium falciparum* is essentially a parasite of the hæmatopoietic organs; its presence in the peripheral blood is far from constant, even during the febrile attacks (35-40 per cent. of the cases); as a general rule it is found in very small numbers in the blood. The preparations must therefore be examined for a long time before concluding that the hæmatozoon is absent.

The parasitic forms found in the blood differ completely according as the patient is suffering from an ordinary febrile attack or a pernicious one.

A. *In the course of the ordinary forms of tropical paludism* the forms met with in the blood belong to two types only; the schizont and the gamete. During the febrile attacks either the schizonts are found alone or the schizonts and gametes simultaneously; in the interval between the attacks only the gametes are found. The appearance of schizonts at this period should indicate that a relapse is imminent.

(*a*) The *schizont* of *Plasmodium falciparum* is to be recognized by the following characters: The corpuscle which it invades is not enlarged, it is not decolorized, but on the contrary often shows a slight overstaining (copper tint); it does not contain Schüffner's dots. The larger and irregular granulations described by Maurer often seem to be absent or at least only to be brought into view by special stains. The parasite itself often appears in the form of a small ring, consisting of a very thin band of protoplasm and surrounding an achromatic zone; at one point the ring is occupied by a grain of chromatin stained a bright red and constituting the karyosome. Frequently this nucleus is double, each grain being connected with the other by a very thin filament of chromatin. The absence of any pigment in the schizonts of *Plasmodium falciparum* is the rule.

(*b*) The *gametes* have a characteristic form. They are the *crescents*. They are constituted by a membrane with a double wall, fairly visible protoplasm and pigment. The latter is sometimes grouped in the centre of the crescent forming a mass which masks the nucleus (macrogametocytes), or on the contrary disseminated irregularly throughout the extent of the element; the nuclear chromatin is then visible in the form of filaments (microgametocytes).

Side by side with non-pigmented schizonts which predominate and sometimes infest in large numbers the same corpuscle, and the crescents which are often present, we may also find: 1. pigmented schizonts of a larger size than the preceding; 2. rosette bodies generally with fourteen merozoites; 3. bodies which occupy an intermediate position between the schizonts and the rosette bodies, or between the schizonts and the gametocytes; they are rounded elements with deeply staining protoplasm, and a large double nucleus enclosing several thick grains of pigment.

3. Plasmodium malariæ

The *Plasmodium malariæ*, the agent of quartan fever, is quite exceptional. It is usually found fairly easily in the blood, either during the ague fits or in the interval. As in the case of *Plasmodium vivax*, the forms found in the same preparation usually belong to different stages of evolution.

The corpuscles invaded are not increased in size; they are not decolorized and do not contain granulations. The parasite appears in the following forms, all of which possess the common feature of being clearly visible owing to *the intensity of the staining* of the *Plasmodium malariæ* which can be stained much more readily than the other hæmatozoa.

(*a*) The young *schizonts* are annular with a thick crown of protoplasm and pigmented. Subsequently they become elongated in the form of a thong, a narrow band, or a pear. Their outlines are very definite, the nucleolus is large and elongated, and the protoplasm dark blue.

(*b*) *The amœboid bodies* are quadrangular in the form of a rectangular body. The nucleolus is usually elongated, the protoplasm contains abundant pigment in the form of large granules, which frequently have a linear distribution, forming a border round the parasite. The slanting quadrangular form is not constant, for some forms are rounded.

(*c*) *The rosette bodies* formed of 6-12 merozoites show a remarkable regularity resembling a daisy in appearance.

	Plasmodium Vivax.	Plasmodium Falciparum.	Plasmodium Malariæ.
Infected corpuscle—			
Size	Enlarged	Normal	Normal
Coloration	Discoloured	Not discoloured	Not discoloured
Granulations	Schüffner's dots	Maurer's dots	Absent
Frequency of blood infection	In 80 per cent. of the cases numerous parasites	In 35 to 40 per cent. the parasites are rare except in pernicious attacks	In 80 per cent. the parasites are rather rare
Evolutional Varieties—			
Schizonts	Chiefly ovoid, protoplasm in fairly thick crown	Rounded, protoplasm in very thin crown	Elongated with very clear outlines
Amœboid bodies	Frequent in the blood, very polymorphous	Absent	Quadrangular
Rosette bodies	Mulberry-shaped with 16 or 20 merozoites	Absent except in pernicious attacks, 8 to 14 merozoites	Daisy form, 6 to 12 merozoites
Gametes	Rounded, larger than a normal corpuscle	Crescent shaped	Rounded. Size of a normal corpuscle
Parasitic formula of the ague fit	Frequent presence of all the forms	Schizonts alone or with crescents Schizonts, rosettes, crescents, and all intermediary forms in the pernicious attacks	Frequent presence of all forms

(*d*) *The gametocytes* are ovoid, richly pigmented, and contain a large nucleus. The macrogametocytes have a much darker protoplasm than that of the microgametocytes. The following table shows the various differential characters of the three plasmodia of malaria.

The examination of a specimen of blood should mean more than a search for the parasites of malaria. It is advisable also to investigate two hæmatological signs, the presence of which is important and serves as a guide to diagnosis in the absence of the parasites. These two signs are: 1. *mononucleosis*, which is especially frequent at the end of an ague fit or in the interval between two fits; 2. the presence of *melaniferous leucocytes*, which is not found till late and requires careful investigation, as the number of melaniferous leucocytes is limited.

THE THICK DROP PROCESS. If it is desirable to make a rapid examination for rare elements, especially crescents, the "thick drop process," advocated by Leishman, can be employed with advantage. Put 3-5 droplets of blood on the slide without making a film of them, but leave them to spread out spontaneously with a diameter of about 5 millimetres. Dry, then hæmolyze the preparation in distilled water; the red cells become dissolved, while the leucocytes and parasites remain intact. Dry again, and stain by one of the methods indicated below.

The elements are generally less finely differentiated, and the schizonts are less definite in outline, but a trained eye can easily recognize them among more or less well-stained leucocytes. The process enables a few parasites to be found readily in a relatively larger quantity of blood.

LAVERAN'S PANCHROME STAIN.—Technique: Do not fix the smear. Spread the undiluted panchrome over the slide to be stained. Cover the slide to prevent evaporation. Leave three minutes for fixation ; then turn the slide over, with the surface to be stained downwards, in a capsule (Laveran's or Petri's), containing the quantity of distilled water corresponding to the quantity of panchrome used. Shake at once, so as to get a good mixture. Leave for fifteen to twenty minutes according to the elements to be stained. Wash in plenty of water. Dry between two cigarette papers. Never use heat for drying.

The panchrome may be more diluted, in which case the time of staining should be prolonged. The staining, for instance, may take twelve hours (a whole night), in a 5 per cent. solution, but in that case, the preparation must first be fixed ten minutes in absolute alcohol.

It is essential that the distilled water should be absolutely neutral.

CHAPTER VIII

TREATMENT[1]

THE various forms of treatment for malaria differ according as the disease is primary or secondary.

I. PRIMARY PALUDISM

Generally speaking, whatever the clinical forms assumed by the febrile attacks, the irregular succession of which constitutes primary paludism, *the principal feature of the treatment at this time should be the energetic administration of quinine.*

The medical officer should realize that summer malaria in Macedonia is a formidable disease, against which the doses of quinine usually employed elsewhere are ineffectual. Their failure is due to many causes, viz., the nature of the pathogenic agent, which in more than 85 per cent. of the cases is the *Plasmodium falciparum*; the hæmatozoon, which offers the most resistance to quinine; the multiple inoculations with the parasite due to the enormous number of the Anopheles; and, lastly, the varied conditions, such as climate, fatigue, and physical overwork, which weaken the resistance of the organism.

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[1] P. Abrami, *Le Paludisme primaire en Macédoine et son traitement. Presse médicale,* March 22, 1917, and *Bull. Soc. Méd. Hôp., Paris,* March 12, 1917.

The aim to be pursued in treating primary paludism is essentially different according as one is dealing with a first attack of fever (paludism in its first invasion), or, on the other hand, subsequent attacks which constitute relapses. This distinction in our opinion is all important, and it is necessary to emphasize its significance.

During the first invasion the doctor's principal aim should be to prevent the formation of gametes. These never appear before the eight or tenth day of the disease. Their presence in the organism entails two serious consequences. In the first place, they are the only forms of the parasite which are capable of propagating the hæmatozoa after absorption by the mosquito. They are, therefore, the only source of a malarial epidemic; without gametes there would be no social paludism. Secondly, those forms which are particularly resistant to quinine tend to make the disease chronic by giving rise to fresh generations of parasites, which are the source of relapses. Without gametes there would be no individual paludism. Before the formation of gametes malaria is an acute disease which can be sterilized by quinine. After the formation of gametes malaria becomes a chronic disease, the cure of which requires a very long time as a rule.

In dealing, therefore, with the treatment of primary paludism, we must discuss successively: 1. The attack in its first invasion. 2. The period of relapses.

1. Paludism in its first invasion.—The treatment of the attack in its first invasion should be *early and intensive*; early, because the sooner the administration of quinine begins, the greater are the chances of killing the parasites before they have had time to change into gametes, and intensive, because small doses of quinine favour the development of these resisting forms.

After the patient has been given a saline purgative (30-40 gm. of sulphate of soda), repeated, if necessary, on the following days, 3 *grammes of quinine a day should be given* throughout the duration of the febrile attack.

Two questions have to be discussed from this point of view; first, that of the manner of administration of this dose; secondly, that of the time when it should be given.

(1) **Mode of administration of quinine.**—The physician has three principal modes of administration at his disposal, *ingestion*, *intramuscular injection*, and *subcutaneous injection*. As regards *intravenous injection*, it remains necessarily an exceptional process, which can only be used in certain hospitals and particularly severe cases, like pernicious attacks.[1]

Ingestion of quinine takes place either in the form of tablets, or by preference in solution (*e.g.* quinine hydrochloride 10 gm., water 400 gm., each tablespoonful containing 50 gm. of quinine). After taking the drug the patient may be given a quantity of fluid (hot tea, weak coffee, ptisan, or lemonade) to diminish the irritating action of the quinine on the digestive mucous membrane.

Ingestion should be reserved for mild cases, in which gastric symptoms (vomiting) or intestinal symptoms (diarrhœa) are absent.

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[1] *v.* Carnot and De Kerdrel, *Paris médical,* December 1916.

It is chiefly indicated during the last days of the febrile attack at the commencement of defervescence.

The doctor should make sure himself that the quinine so prescribed has really been taken. Tanret's reagent readily enables the drug to be detected in the urine.

Intramuscular or subcutaneous injection of solutions of quinine constitutes the best method of treatment of paludism in its first invasion, provided that certain strict rules are observed, the neglect of which renders the method illusory or even dangerous.

a. Choice of solutions.—The great objection to the ordinary solutions (solution of quinine and antipyrine or quinine and urethane) is that they are hypertonic from excessive concentration of quinine. Moreover, the solution of quinine and antipyrine, which contains 0·30 gm. of antipyrine to 0·50 gm. of quinine, leads to the injection of 0·80 gm. of antipyrine daily into patients with delicate kidneys and a vascular system in a state of hypotension. Owing to their hypertonic nature, the absorption of these solutions is certainly slower and less complete than when given by the gastric route; and this defect in our opinion is sufficient to condemn a method whose chief object is to lead to more rapid absorption. Lastly, each injection often gives rise to a painful inflammatory nodule, in which the quinine is retained sometimes indefinitely; on repetition of the injection the caustic action of the quinine renders the patient liable to necroses and more or less extensive and deep-seated abscesses, which are very slow in healing after they have been incised.

Diluted solutions of quinine should be employed, so as to reduce to a minimum the caustic nature of the product and to facilitate its rapid absorption. Roux's syringe should be substituted for that of Pravaz in giving the injections. One of us has recommended the use of the following two solutions :—

1. Quinine hydrochloride, 10 gm.
   Antipyrine, 1·50 gm.
   Distilled water, 200 gm.
2. Quinine hydrochloride, 10 gm.
   Urethane, 3 gm.
   Distilled water, 200 gm.

According to the experience of the inspector-general Grall and Dr Castellani there is a real advantage in sterilizing solutions of quinine by *tyndallization*, as sterilization at 120° C. is one of the chief causes of the necroses seen after injection.

In order to check the depressing action of quinine on the cardio-vascular system we add to the above solutions before injection the contents of an ampoule of a milligramme of adrenalin to each 30 c.c. of the solution.

b. Technique.—Injection of quinine, whether intramuscular or subcutaneous, requires *most careful antiseptic precautions*. A large number of complications (abscesses and sloughing) are due to neglect of this elementary rule. The instruments (syringes and needles) should be sterilized in the autoclave or by prolonged boiling. The needle should be at least 5 cm. long and should be sterilized after each injection. The operator's hands should be carefully washed, and the patient's skin sterilized with tincture of iodine which, it should be noted, does not act until four or five minutes after being applied.

(*a*) *Intramuscular injections.*—Intramuscular injection should only be made at the seat of election, *i.e.* in a region where the sciatic nerve cannot be injured directly or affected by inflammation. This area is limited above by the iliac crest, and below by a horizontal line passing through the upper extremity of the natal cleft.

The needle, which should be at least 5 cm. long, should be plunged by itself vertically and deeply into the body of the muscle; the injection should be given very slowly, and as soon as it is finished, the needle should be withdrawn by a single quick movement. Injections should not be repeated in regions which are the seat of nodosities or inflammatory swelling.

c. Subcutaneous injections. — A subcutaneous injection should only be given with a dilute isotonic solution of quinine.

It should only be given in the regions of election, viz., the back of the throat, the flanks, or the abdomen.

It should be given into the subcutaneous cellular tissue, as penetration of the fluid into the dermis is liable to cause necrosis. The needle, which should be a least 5 cm. long, should be thrust in separately first of all, and it is only after it has been found to be freely movable in the cellular tissue that the syringe is fitted on and the injection is given slowly. We have no hesitation in giving the preference to subcutaneous injection; when performed carefully, it hardly ever has any complications.

(2) **Time for administration of the quinine.**—The three grammes of quinine should be given *in two doses:* 1.50 *gm. morning and evening when intramuscular or subcutaneous injections are employed; or in three doses* (1 *gm. in the morning,* 1 *gm. about noon, and* 1 *gm. in the evening*), *when they are taken by mouth.*

No account of the law of the hour is taken in adopting this method. This law is inapplicable to paludism in its first invasion, as seen in Macedonia; the biological factors which give rise to it were not found in our patients, and the pharmaco-dynamical factors which possibly justify it when the ordinary methods of treatment are in use do not hold good when isotonic solutions are employed. Each of these two points requires further consideration.

Experiments admitting of no dispute have established that quinine is most active on the merozoites which are derived from the rupture of the rosette bodies (biological conclusion). As this rupture coincides with the onset of the febrile attack, it is important that the quinine should reach its maximum concentration in the blood at this precise moment.

Investigations carried out many years ago for the purpose of establishing the cycle of the absorption of quinine proved that the absorption reached its height at the end of six hours (pharmacodynamic conclusion). As the result of these two conclusions, the following law was established: quinine should be given from six to eight hours before the onset of the attack. This is the law of the hour.

This law is only applicable to exceptional cases. Owing to the large number of infecting bites which are usually inflicted, malarial individuals are carriers of several generations of plasmodia, which evolve simultaneously in the system, each according to its definite cycle. The result of this, as is clearly proved by examination of the blood, is that parasites of very different ages are *present in the organs and the blood at a given moment.* The law of the hour, which is applicable to cases in which only one or at most two alternating generations of parasites are present, cannot and ought not to be observed in the cases which we have to treat.

Secondly, the pharmacodynamic idea of the optimum absorption of quinine in six hours' time is perhaps true in cases of administration of the drug by mouth or of injection of *hypertonic solutions*, but it is quite wrong when subcutaneous injections of *isotonic* solutions are given. Their absorption is extremely rapid. In less than half an hour after injection the patient feels the effects of quinine intoxication, and in less than an hour the destruction of the circulating plasmodia, even of the adult forms, is obvious, as can easily be seen in patients whose blood literally swarms with parasites of all ages.

Lastly, it is impossible to take a law of the hour into account in a disease in which the febrile attacks are characterized by continuous or subcontinuous fever without any perodicity in the evolution of the paroxysms.

II. Period of Relapses and Second Attacks

The malarial subject, in whom the abortive treatment of the first invasion has failed and who has consequently become a gamete carrier, is henceforth doomed to suffer from a chronic disease. This disease consists of a more or less close succession of febrile relapses due to the production of generations of plasmodia derived from cystic germination and separated by intervals of apyrexia. Moreover, in addition to relapses, there is the possibility of more or less frequent reinoculations. What treatment should be adopted in chronic primary paludism—

1. During the febrile relapses ?
2. During the intervals of apyrexia ?

A. **Treatment of relapses.**—The relapse should be attacked energetically by quinine. But the doctor's aim should no longer be to endeavour to produce an immediate sterilization of the system, as this can no longer be obtained in most cases. All that one can ask of quinine is that it should shorten the febrile attack, attenuate its effects, and prevent pernicious attacks by destroying as large a number as possible of generations of plasmodia. The cure of the disease can only be obtained by successive courses of treatment, and often requires a very long time.

The treatment varies according to the character of the relapse.

1. In most cases, the relapse assumes the type of *remittent continued fever*, its duration varying from four to six, eight or ten days. The subintrant attacks which constitute it do not show any hourly periodicity, but as a rule the febrile maxima occur in the second half of the night.

(*a*) *When the fever does not reach a high level* (104° F.), and the general condition remains satisfactory; when the examination of the blood shows only a few plasmodia or remains negative, we prescribe 2 gm. of quinine (hydrochloride) daily in two doses, viz., 0·50 gm. about 8 a.m. and 1·50 gm. at about 6 p.m. Unless there is gastric intolerance, which resists ipecacuanha or sulphate of soda, the drug is given by mouth in solution or in cachets until defervescence. Otherwise we have recourse to hypodermic injections of isotonic solution. In every case adrenalin in doses of a milligramme morning and evening is associated with the specific treatment.

(*b*) *When the febrile attack is severe*, or if the examination of the blood indicates a large number of parasites, we raise the dose of quinine to 3 gm., until the temperature does not exceed 100·4° F., which occurs as a rule in two or three days. These 3 gm. are given daily subcutaneously in doses of 1·50 gm. morning and evening. We then lower the daily dose to 2 gm. given by mouth, as in the previous case.

(*c*) *Lastly, in cases of pernicious attacks*, the course to be taken differs according as we are dealing with an algid attack or an attack of the comatose type. In the *algid attack* the danger lies not in the invasion of the parasites, which may not even be present in the blood, but in the sudden cardio-vascular collapse. In such cases the treatment urgently required is *intravenous injection of adrenalin in normal saline solution* (2 milligrammes of adrenalin in 500 to 1000 gm. of normal saline). Intravenous injection, which is the only efficacious method in subjects in whom the entire vascular system is in a state of collapse, and in whom no absorption by the subcutaneous route can be hoped for, intravenous injection, we say, has enabled us to save four out of six of our patients ; in two of them *signs of apparent death had already been present for more than five minutes ;* the injection was accompanied by artificial respiration and recovery took place. In the algid attack, therefore, treatment by quinine is of secondary importance, and need only be used after the above treatment has been instituted.

In the *comatose attack* the danger comes from the presence of the parasites in the blood. Septicæmia was a constant feature in our patients, and reached such a degree that in blood preparations it was easier to count the number of healthy corpuscles than of those infected by the *Plasmodium falciparum.* In other districts comatose attacks without infection of the blood have been repeated, as well as comatose attacks due to the *Plasmodium vivax*, but we have not personally come across such cases. All our cases were caused by the *Plasmodium falciparum*, and presented a massive septicæmia. In such cases treatment should simultaneously combat the septicæmia by the use of quinine, and its general effects by means of revulsives, cardiac stimulants, etc. The necessity of administering quinine in such cases by injections is generally admitted; rapid action is needed. One of us, after four trials, abandoned the intravenous method, as when performed on subjects with hyperpyrexia the injection caused phenomena of shock which it seemed advisable to avoid. We make use of subcutaneous injections; 1 gm. of quinine being given on admission to hospital, 1 gm. four hours later, and another 1 gm. in another four hours. The injections are repeated in the same doses until the comatose state completely disappears; they are then reduced to two a day, each consisting of 1 gm., until recovery takes place.

2. In some cases, which are much less frequently seen, and hardly ever until the infection is of several months' duration, the relapses assume the form of *several series of quotidian attacks* separated by periods of apyrexia of variable duration. These forms generally prove very difficult to treat. It was only *by injecting 3 gm. a day, in two doses of 1·50 gm.*, and from the onset of the febrile attack, that we succeeded in reducing the number of attacks to two or three.

Of course *the management of relapses does not merely consist of treatment by quinine.* According to the predominance or association of certain symptoms, it may also be necessary to treat pulmonary, gastric, intestinal, or hepatic phenomena, which import a special physiognomy to each febrile attack. One of the most important of these associations, both as regard prognosis and treatment, is in our opinion *dysenteriform enteritis*. Owing to its extreme prevalence during the months of September and October, its tenacity, its resistance to ordinary treatment, such as quinine, and its frequent relapses, it represented one of the most serious complications of malaria; it prolongs and aggravates the organic dissolution and leads to early cachexia. It should be combated as soon as it appears. One of us has shown in association with C. Foix that in most cases ordinary serum treatment applied early constitutes a very successful curative method. Injection of 60-80 c.c. of horse serum (anti-diphtheritic or anti-tetanic as well as anti-dysenteric serum), repeated if necessary the following day, may cause the most acute dysenteric syndromes to disappear in forty-eight hours, and reduce the stools from thirty to forty down to one or two in a day.

B. **Treatment of the intervals.**—As soon as the relapse is over *we suspend the administration of quinine* until the following relapse. The reasons which determined us to do this are numerous. First of all, quinine treatment carried out during the period of apyrexia with the object of preventing the approaching relapse invariably proved ineffective. Whatever the daily dose of quinine, its method of administration, and the duration of the cure, we never prevented the return of the attacks, but they always occurred during the course of the preventive treatment. Some of our patients took regularly every evening 1 gm., 1·50 gm., or even 2 gm. of quinine in solution or in cachets, others were given 1·50 gm. for five days, and then after two days' interruption resumed the treatment; to others we gave 2 gm. every two days, and in others the preventive treatment was started five days before the presumed date of the return of the fever, but in every case the attempt to prevent the relapses failed.

Moreover, there seemed to us to be no doubt that *prolonged use of quinine in doses of* 1 *gm. and above presented real dangers.* Anorexia and digestive disturbances set in rapidly, and interfered with the taking of nourishment which is one of the essential elements of the treatment, while anæmia and a tendency to œdema increased with the prolongation of quinine treatment.

Lastly, relapses occurring in subjects who have been taking quinine for a long period are generally much less affected by larger doses of the drug, just as if the hæmatozoon had really acquired *resistance to quinine.*

We have, therefore, completely abandoned the administration of quinine during the intervals between the relapses. The period of apyrexia of varying duration which follows the end of a relapse, is a period of relative immunity.

Advantage should be taken of it to repair as quickly as possible the losses of the organism and to enable it to resist the following attack. Experience having shown that relapses are more frequent and severe when the patient is anæmic and exposed to fatigue and privations, rational treatment should comprise: 1. *absolute rest*; 2. *substantial nourishment*; 3. *reconstitution of the blood by iron and arsenic.* An all important precaution must be added, viz., to protect the patient from fresh virulent inoculations by means of the *mosquito net.*

In those rare cases where the mechanical protection provided by the mosquito net is not available, it is obvious that *between the relapses* the malarial subject should obey the rule of preventive quinine treatment (0·50 gm.-0·75 gm. of quinine per diem).

To sum up, the treatment of chronic primary paludism comprises *a series of sterilization cures by quinine*, strictly reserved for the febrile attack, and alternating with *tonic cures to build up the system.*

The treatment of primary paludism which has become chronic, is in most cases only a palliative treatment; it is only exceptionally that a recovery from the disease takes place in a country infested with malaria. Rapid improvement, on the other hand, takes place in healthy districts. Early repatriation of the patients is a measure the necessity of which appears to admit of no discussion.

II. SECONDARY PALUDISM

In winter and spring malaria changes in character. The febrile attacks assume the form of frank isolated paroxysms which occur with a certain periodicity, being sometimes quotidian and sometimes tertian, or septan, bi-septan, or tri-septan.

Examination of the blood at this paroxysmal period which characterizes secondary paludism reveals an inversion of the parasitic formula; preparations show that the *Plasmodium falciparum*, the predominating agent of æstivo-autumnal malaria, has been superseded by the *Plasmodium vivax*, the principal cause of the malaria of the winter and spring, a season when the disease is much less dangerous and reacts better to quinine.

We will confine ourselves to a description of the general rules of a treatment which has long been established. The treatment applies first to the ague fits, and secondly to the intervals.

1. **Treatment of the ague fits.**—The ague fit should be treated energetically, 2 *gm. of quinine* as an ordinary dose should be given in the twenty-four hours. These 2 gm. may be administered :—

(1) By intramuscular or subcutaneous injections: 1 gm. in the morning and 1 gm. at night.

(2) By ingestion (in tablets or solution), and in that case one must always make sure that the dose prescribed is really taken. The mode of administration of these 2 gm. really matters little. Some give 0·50 gm. in the morning and 1·50 gm. at night, others 1 gm. in the morning and 1 gm. at night, while others prefer fractional doses, *e.g.* 4 doses of 0·50 gm. or even 0·25 gm. eight times in the twenty-four hours.

In the case of quotidian attacks the administration of quinine should be continued regularly until the fever disappears, and in the case of tertian attacks until the disappearance of the series of ague fits. In all cases the treatment should be continued in the same doses for at least two days after the commencement of final apyrexia.

2. **Treatment of the intervals.**—When apyrexia is established, the patient should undergo *discontinuous quininization* according to Laveran's method of successive treatments. There are various forms of this treatment; all yield the same results. The following are some of the formulæ:—

(1) *One day of quinine and one day of rest*, one day of quinine and one of rest, and so on, for six consecutive weeks. On the quinine days the drug is given in a single dose of 1 gm. or 1·50 gm. by mouth (in tablets or solution), or in two doses (0·50 gm. in the morning and 0·50 gm. or 1 gm. at night) or in four or five doses.

When an ague fit occurs in the course of treatment, the dose is raised to 2 gm. on the day of the fit and the two following days.

(2) *Job's method.*—During the first week: six days of quinine and one day's rest. During the second week: five days of quinine and two days' rest. During the third week: four days of quinine and three days' rest. During the fourth to the eighth weeks: three days of quinine and four days' rest.

On the quinine days the drug is ordered in doses of 1 gm. (a tablet of 0·25 gm. at 8 a.m., one at 10 a.m., one at noon, and one at 2 p.m.).

(3) *Carducci's method.*

1st week.

1st and 2nd day of apyrexia, 1 gm. of quinine daily.

3rd and 4th day, no quinine.
5th and 6th day, 1 gm. of quinine.
7th day, 1·50 gm. of quinine.

2nd, 3rd, 4th, 5th and 6th weeks.

8th day, 1 gm.
9th, 10th, 11th, 12th day, no quinine.
13th and 14th day, 1 gm. of quinine.

There is no need to insist on the advantage of associating with quinine treatment absolute rest, abundant nourishment, arsenic and iron.

(4) *The Italian "sterilizing" method.*—The Italian medical officers advocate the following treatment:—

1st week.

2 gm. of quinine daily.

2nd week.

One day of rest, followed by a cold bath, then 2 gm. of quinine daily.

Final cessation of quinine treatment, followed by a cold bath.

If this bath does not give rise to another ague fit, the patient is considered to be cured.

If a fresh fit occurs, the treatment must be started again.

In view of the intensity of malaria in Macedonia, Castellani and the Italian writers have recommended even 3 gm. daily during the first few days.

Ravaut's method.—Ravaut has made trial of cacodylate of soda and obtained interesting results; but it has to be employed in large doses (20-30 cgm. daily) and, of course, combined with quinine. The following is the method which he has had carried out in several hospitals.

A subcutaneous injection of 0·20 or 0·30 gm. of cacodylate of soda is given daily for three or four days running. The following two or four days 2 gm. of quinine in cachets are to be taken by mouth. Then the injections of cacodylate are to be resumed, and so on for at least a month, without paying any attention to the febrile attacks.

Lastly, Ravaut, in view of the signs of suprarenal insufficiency which he found almost invariably present, advocates the addition of adrenalin, which is very efficacious either in the form of injections or in the form of solution (twenty drops daily of the one in 1000 solution).

This treatment can be carried out by anyone, does not present any danger, and gives very superior results to those obtained by quinine alone.

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Previous to the present war no stomatologist or surgeon possessed any very extensive experience of this subject. Claude Martin, of Lyons, who perhaps gave more attention to it than anyone else, aimed particularly at the restoration of the occlusion of the teeth, even at the risk of obtaining only fibrous union of the jaw. The authors of the present volume take the contrary view, maintaining that consolidation of the fracture is above all the result to be attained. The authors give a clear account of the various displacements met with in gunshot injuries of the jaw and of the methods of treatment adopted, the latter being very fully illustrated.

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Grounding his remarks on a considerable number of observations, Professor Lagrange arrives at certain conclusions which at many points contradict or complete what we have hitherto believed concerning the fractures of the orbit: for instance, that traumatisms of the skull caused by fire-arms produce, on the vault of the orbit, neither fractures by irradiation nor independent fractures; that serious lesions of the eye may often occur when the projectile has passed at some distance from it. There are, moreover, between the seat of these lesions (due to concussion or contact) on the one hand, and the course of the projectile on the other hand, constant relations which are veritable clinical *laws*, the exposition of which is a highly original feature in this volume.

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Of all the medical works which have appeared during the war, this is certainly one of the most original, both in form and in matter. It is, at all events, one of the most individual.

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The authors review, in succession, the Clinical details, the Epidemiology, and Prophylaxis of *Dysenteries*, *Cholera*, and *Typhus*. In the section dealing with *Prophylaxis*, in particular, will be found practical advice as to the special hygiene possible in the case of large collections of people placed in conditions favourable to the development of these diseases.

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Of all the infections which threaten our wounded men, tetanus is that which, thanks to serotherapy, we are best able to prevent. But serotherapy, when it is late and insufficient, may, on the other hand, tend to create a special type of attenuated and localised tetanus ; in this form the contractions are as a general rule confined to a single limb. This type, however, does not always remain strictly monoplegic ; and if examples of such cases are rare this is doubtless because physicians are not as yet very well aware of their existence.

We owe to MM. Courtois-Suffit and R. Giroux one of the first and most important observations of this new type ; so that no one was better qualified to define its characteristics. This they have done in a remarkable manner, supporting their remarks by all the documents hitherto published, first expounding the characteristics which individualise the other atypical and partial types of tetanus, which have long been recognized.

The preventive action of anti-tetanic serum should not cause us to disregard its curative action, the value of which is incontestable. However, a specific remedy, even when a powerful specific, cannot act upon all the complex elements which constitute a disease ; and tetanus presents itself, in the first place, as an affection of the nervous system. To contend with it, therefore, a symptomatic medication should come to the aid of a pathogenic medication.—*Professor Widal.*

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Dr. Thibierge, whose previous labours guarantee his peculiar competence in these difficult and important questions, has, in writing this manual, very notably assisted in this work.

But the treatment of syphilis has, during the last six years, undergone considerable modifications; the new methods are not yet very familiar to all physicians; and certain details may no longer be present to their minds. It was therefore opportune to survey the different methods of treatment, to specify their indications, and their occasionally difficult technique, which is always important if complications are to be avoided. It was necessary before all to state precisely and to retrace, for all those who have been unable to follow the recent progress of the therapeutics of venereal diseases, the characters and the diagnostic elements of the manifestations of syphilis.

Of late years, moreover, new methods of examination have entered into syphilitic practice, and these were such as to merit exposition while the old elements of diagnosis were recalled to the memory.

In short, this little volume contains those essentials which will enable the physician to accomplish the *entire* medical portion of his anti-syphilitic labours; it will also provide him with the elements of all the medical and extra-medical advice which he may have to give the civil and military authorities in order to arrive at an effective prophylaxis of this disease.

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